International Urogynecology Journal
https://doi.org/10.1007/s00192-022-05149-x

ORIGINAL ARTICLE

A pilot randomized controlled trial of vaginal estrogen on postpartum atrophy, perineal pain, and sexual function

Pamela E. Smith[1] · Eric M. McLaughlin[2] · Lopa K. Pandya[3] · Erinn M. Hade[4] · Courtney D. Lynch[5] · Catherine O. Hudson[6]

Received: 3 December 2021 / Accepted: 13 February 2022

Abstract

Introduction and hypothesis Vulvovaginal symptoms following perineal laceration may be worsened by atrophy related to decreased estrogen. Our objective was to evaluate the effect of local estrogen therapy in this setting.

Methods We conducted a single-center, pilot, randomized, placebo-controlled trial of local estradiol in primiparous women with a second-degree or greater perineal laceration following a term vaginal delivery. Participants were randomized to twice weekly estradiol or placebo cream from delivery through 3 months postpartum. The primary outcome was a validated measure of vulvovaginal symptoms at 12 weeks postpartum. Secondary outcomes included measures of perineal pain, quality of life, sexual function, ease of use, likelihood of continued use, and adverse events.

Results We planned to enroll 70 women; however, due to human subjects research restrictions related to the COVID-19 pandemic, enrollment was stopped early. A total of 59 women were randomized, 31 to the estradiol group and 28 to the placebo group. Nearly all participants (95%) were followed through 12 weeks with suggestion of marginal improvement in Vulvar Assessment Scale scores [-0.10; 90% CI = (-0.20, 0.01)] in those randomized to estradiol compared to placebo. Local estradiol was not associated with improvement in other measures, and only one non-serious adverse event was observed.

Conclusions In primiparous women with a perineal laceration, use of local estradiol showed minimal clinical benefit in vulvovaginal atrophy and related symptoms but appears to be acceptable and safe for postpartum use. Larger adequately powered trials enrolling a diverse group of postpartum women are needed to affirm these findings.

Keywords Vaginal estrogen · Postpartum atrophy · Pelvic floor

Introduction

Dyspareunia and perineal pain are well-known sequelae after vaginal delivery [1, 2]. However, the contribution of postpartum vaginal atrophy to these issues is largely unknown. Postpartum vulvovaginal atrophy (VVA) may occur because of relative estrogen deprivation, which can be exacerbated by breastfeeding [3]. The use and efficacy of low-dose vaginal estradiol for the genitourinary syndrome of menopause is well established [4–6]. However, there is a paucity of data regarding the prevalence of postpartum vulvovaginal symptoms and the efficacy of vaginal estradiol in this population.

Most recent studies investigating postpartum dyspareunia and pelvic pain have reported patient-reported data regarding symptoms, timing of return to coitus, and measures of pelvic floor muscle function including vaginal resting pressure and pelvic floor muscle strength [7, 8]. Few studies have commented on the prevalence of postpartum VVA. In

✉ Pamela E. Smith
pamela.e1.smith@kp.org

[1] Kaiser Permanente, Central Valley Area, 4601 Dale Road, Modesto, CA 95356, USA

[2] Department of Biomedical Informatics, Center for Biostatistics, The Ohio State University, 200 Lincoln Tower, 1800 Cannon Drive, Columbus, OH 43210, USA

[3] Female Pelvic Medicine and Reconstructive Surgery, University of Illinois at Chicago, 820 S Wood St, CSN (MC808), Chicago, IL 60612, USA

[4] Department of Population Health, Division of Biostatistics, NYU Grossman School of Medicine, 180 Madison Ave, Suite 5-53, New York, NY 10016, USA

[5] Department of Obstetrics & Gynecology, The Ohio State University, 395 W 12th Ave, Room 580, Columbus, OH 43210, USA

[6] Wellstar Urogynecology, 4900 Ivey Rd NW, Suite 1320, Acworth, GA 37363, USA

Published online: 20 April 2022

1991, Wisniewski and Wilkinson described a 17.2% prevalence of VVA in a prospective study of women at 4 weeks postpartum [9]. Of those women with VVA, 80% reported dyspareunia compared to 12.9% of those women without VVA. Although not designed to evaluate treatment efficacy, the authors reported an improvement of symptoms with the application of conjugated estrogen vaginal cream. Similarly, case reports have described the use of vaginal estradiol cream in the treatment and surgical management of postpartum genital adhesions and agglutination [10].

Investigative and clinical use of vaginal estradiol has been limited to the genitourinary syndrome of menopause [5, 11]. Because VVA can be present in both menopausal and postpartum states, it is reasonable to assume that many of the benefits seen with vaginal estradiol use in menopausal women may translate to postpartum use. To date, there are no published comparative trials evaluating low-dose estradiol use in the treatment of VVA in the postpartum period. Our pilot randomized, placebo-controlled trial aimed to evaluate the short-term efficacy, acceptability, and safety of local estradiol in the treatment of postpartum genitourinary symptoms in primiparous women with perineal lacerations following a term vaginal delivery.

Materials and methods

Study design and population This pilot double-blind, randomized, placebo-controlled trial was performed at The Ohio State University Wexner Medical Center between October 2018 and September 2020. This study was reviewed and approved by the Ohio State Biomedical Institutional Review Board prior to initiation. Eligible participants included primiparous women ≥ 18 years old with at least one prenatal visit within the medical system who underwent a term vaginal delivery (≥ 37 weeks and 0 days) associated with a second-degree perineal laceration or greater. Patient charts were pre-screened for potential eligibility, and patients were then approached in person by the study team, provided information about the study, and asked to complete a screening questionnaire prior to hospital discharge. Individuals were excluded if they had an allergy to estradiol cream or its constituents, had a cesarean delivery, had a vaginal delivery associated with an intrauterine fetal demise or neonatal death, were unable to complete questionnaires in English, or were unable to adhere to the study protocol and apply vaginal cream independently. Individuals with the following conditions were also excluded: undiagnosed abnormal vaginal bleeding, known or suspected estrogen-dependent neoplasia, active or history of deep venous thrombosis or pulmonary embolism, active arterial thromboembolic disease, known liver dysfunction or disease, or known thrombophilic disorders. Patients who met the eligibility criteria and provided informed consent for participation were scheduled for a randomization visit within 7 business days of delivery.

Data collection All study data were collected using the Research Electronic Data Capture (REDCap) program [12]. All participants attended an in-person visit at which randomization occurred and the study drug was provided. In-person study visits were also scheduled for 6 and 12 weeks postpartum. Participants who were unable to attend those visits in person were emailed a secure link to complete the visit questionnaire and scales. At 6 months postpartum, participants were emailed a link to complete their last set of study forms and were contacted via telephone to collect the Vulvar Assessment Scale score.

Intervention Participants were randomized 1:1 in permutated blocks of size two or four stratified by perineal laceration degree (second degree versus third and fourth degree). The intervention arm received estradiol cream (Mylan estradiol vaginal cream, USP, 0.01%) while the placebo arm received a placebo cream (Professional Compounding Centers of America #30-3641 Base, VersaBase® Cream). Participants were instructed to insert 1 g of study cream intravaginally twice weekly for a total of 12 weeks.

Outcome measures The primary study outcome was the Vulvar Assessment Scale (VuAS) at 12 weeks postpartum. The VuAS was developed to assess subjective and objective outcomes related to VVA in women with breast cancer and survivors and has been validated and used in various populations [13–16]. Key secondary outcomes included the Vaginal Assessment Scale (VAS) and the Vaginal Health Assessment (VHA). While the VAS is also a patient-reported outcome, the VHA is a physician-based assessment that was performed by a Female Pelvic Medicine and Reconstructive Surgery specialist at the 6 and 12 week visits. Additional secondary patient-reported outcomes at 6 and 12 weeks included the Numerical Rating Scale (NRS) to assess perineal pain, Edinburgh Postnatal Depression Scale (EPDS), Urinary Distress Inventory-6 (UDI-6), Fecal Incontinence Severity Index (FISI), and Female Sexual Function Index (FSFI) [17–21]. Satisfaction, ease of use, and likelihood of continued use were also assessed via survey at the 6 and 12 week follow-up [22]. Adverse events were reported throughout the study period.

Sample size considerations Existing data regarding the primary outcome (VuAS range 0–3) suggested that the average score in those untreated would be 0.8 (SD 0.8) [22]. Given these data, target enrollment was set at 70 participants with an expected attrition rate of 20% based on previous studies performed in this population at our institution. The expected number of patients who would complete their 12-week

follow-up visit was 56. As this pilot trial was planned to provide a preliminary estimate of efficacy, we expected to have 75% power to identify a 50% lower VuAS score (from 0.8 to 0.4) for estradiol, with 10% two-sided type I error with the planned sample size and attrition rate.

Analytic plan Demographic and baseline characteristics of all participants were summarized. The primary outcome, VuAS score at 12 weeks, was compared and reported regardless of treatment adherence (intent-to-treat analysis). An additional sensitivity analysis was performed for the primary outcome to exclude patients who did not adhere to the recommended treatment. Non-adherence was defined as self-reported discontinuation of treatment. Differences between treatment groups were estimated using linear regression, adjusting for stratification factor of laceration degree. Mean differences from the regression analysis, along with the corresponding 90% confidence intervals, were reported. Additional survey scores and other time points were considered secondary outcomes and were analyzed in the same fashion as the primary outcome. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

A total of 2604 women were assessed for eligibility. Fifty-nine participants were enrolled and randomized (31 to estradiol, 28 to placebo) (Supplementary Fig. 1). Baseline demographic, clinical, and delivery characteristics were not notably different among the study groups (Table 1). The majority of the cohort was non-Hispanic White (76%), and the average age of patients was 28.6 years (SD 4.6). Most patients had private insurance (76%) and were college graduates or above (73%). Fifty-two women (88%) experienced a second-degree laceration, seven women experienced an obstetric anal sphincter injury (12%), and four women (7%) had an operative (forceps or vacuum) delivery. None of the women developed a wound complication or required surgical care postpartum.

The overall follow-up rate for the primary outcome at 6 weeks, 12 weeks, and 6 months were 94.9%, 94.9%, and 89.8%, respectively. Over the course of the study, six participants did not follow the intervention as prescribed (one in the estradiol arm and five in the placebo arm); all were included in the primary intent-to-treat analysis. Of those who did not follow the intervention course as prescribed, one did not begin treatment, two stopped after 1 week, one stopped after 2 weeks, and two stopped treatment after 4 weeks.

The primary and secondary outcomes by treatment allocation are summarized in Table 2 with the differences between estrogen and placebo adjusted for laceration degree. For the primary outcome, mean VuAS score at 12 weeks was lower in the estradiol arm compared to the placebo arm [mean difference: -0.10; 90% CI = (-0.20 to 0.01)]. To examine the impact of treatment adherence on this finding, we performed a sensitivity analysis with similar results (Table 3). There were six participants who were non-adherent to the study protocol, and all were removed in the sensitivity analysis. Three participants did not have data available for the primary outcome (three in the estradiol arm, zero in the placebo arm).

Secondary outcomes did not indicate improvements for those randomized to estradiol versus placebo at each follow-up time point. Mean (standard deviation) quality of life and sexual function measures for the entire cohort at 12 weeks were as follows: 0.34 (0.38) for VuAS, 4.07 (3.34) for EPDS, 8.0 (18.1) for UDI-6, 15.9 (13.3) for FISI, and 22.9 (9.8) for FSFI. No clinically meaningful differences were found between randomized group scores for the any of these measures. The mean FSFI full scale score for the entire cohort at 6 weeks was lower (12.5, SD 10.1) compared to the mean score at 12 weeks (22.9, SD 9.8) and 6 months (23.6, SD 9.0). These differences were noted to be similar across both treatment groups. At 12 weeks, no patients reported pain scores > 1 on the NRS scale regarding perineal discomfort.

Participant satisfaction, ease of use, and study drug adherence were assessed at 6 weeks, 12 weeks, and 6 months via Likert scales (Table 4). At week 12 in the estradiol arm, the majority (52%) of women reported being "very satisfied" with the product compared to 33% of women in the placebo group. Most participants in both groups found it "very easy" to use. Participants in the estradiol arm reported increased adherence with treatment, 52% (14/27) reported their perineum felt "very much better," and 58% (15/26) reported using the medication as prescribed "all of the time." In comparison, in the placebo arm, 33% (9/27) of women reported being "very satisfied" with the product, 52% (14/27) found it "very easy" to use, 31% (8/26) reported their perineum felt "very much better," and 33% (9/27) reported applying the medication as prescribed "all of the time."

Women were queried regarding their infant feeding practices at the scheduled study intervals. At 12 weeks participants most often reported feeding their infant via breastfeeding and pumped milk (46%; 25/54), followed by formula (24%; 13/54), breast milk and formula (22%; 12/54), and breastfeeding alone (7%; 4/54). This pattern was similar between cohorts. In the estrogen cohort specifically, participants at 12 weeks most often reported feeding their infant via breastfeeding and pumped milk (48%; 13/27), followed by formula (37%; 10/27) and breast milk and formula (7%; 2/27) as well as breastfeeding alone (7%; 2/27).

While the overall follow-up rate for the primary outcome was 94.9% (56/59) at 12 weeks, slightly fewer than

Table 1 Demographic and clinical characteristics overall and by treatment allocation*

	Total ($N = 59$)	Placebo arm ($N = 28$)	Estradiol arm ($N = 31$)
Age (years), mean (SD)	28.6 (4.6)	29.3 (5.1)	28.0 (4.1)
BMI			
Normal weight (18.5–24.9)	18 (31%)	7 (25%)	11 (35%)
Overweight (25–29.9)	21 (36%)	11 (39%)	10 (32%)
Obese (30+)	20 (34%)	10 (36%)	10 (32%)
Race/ethnicity			
White non-Hispanic	44 (76%)	18 (67%)	26 (84%)
Black non-Hispanic	5 (9%)	3 (11%)	2 (6%)
Hispanic	6 (10%)	5 (19%)	1 (3%)
Other race/ethnicity	3 (5%)	1 (4%)	2 (6%)
Insurance type			
Self-pay/uninsured	5 (8%)	3 (11%)	2 (6%)
Government- assisted	9 (15%)	4 (14%)	5 (16%)
Private	45 (76%)	21 (75%)	24 (77%)
Education level			
High school graduate	9 (15%)	3 (11%)	6 (19%)
Some college	7 (12%)	3 (11%)	4 (13%)
College graduate	22 (37%)	9 (32%)	13 (42%)
Graduate degree	21 (36%)	13 (46%)	8 (26%)
Marital status			
Single	8 (14%)	4 (14%)	4 (13%)
Married	41 (69%)	21 (75%)	20 (65%)
Domestic partner	10 (17%)	3 (11%)	7 (23%)
Depression	13 (22%)	7 (25%)	6 (19%)
Laceration type			
Second degree	52 (88%)	25 (89%)	27 (87%)
Third or fourth degree	7 (12%)	3 (11%)	4 (13%)
Birth weight (kg), mean (SD)	3.5 (0.3)	3.6 (0.3)	3.4 (0.4)
Gestational age (weeks), mean (SD)	39.6 (1.1)	40.0 (1.1)	39.3 (1.0)
Duration of ruptured membranes (hours), median [Q_1-Q_3]	8.1 [4.4–16.4]	7.7 [4.5–12.5]	9.7 [2.8–20.0]
Second stage of labor (hours), median [Q_1-Q_3]	1.2 [0.5–2.3]	1.0 [0.5–2.3]	1.3 [0.8–2.5]
GBS colonization	9 (15%)	5 (18%)	4 (13%)
Chorioamnionitis intrapartum	2 (3%)	0 (0%)	2 (6%)
Antibiotics in labor	9 (15%)	5 (18%)	4 (13%)
Diabetes			
Gestational	4 (7%)	2 (7%)	2 (6%)
Pregestational	1 (2%)	0 (0%)	1 (3%)
Shoulder dystocia	2 (3%)	1 (4%)	1 (3%)
Operative delivery	4 (7%)	3 (11%)	1 (3%)
Episiotomy	6 (10%)	3 (11%)	3 (10%)
Obstetric Anal Sphincter Injury (OASIS)	7 (12%)	3 (11%)	4 (13%)
Antibiotics postpartum	7 (12%)	2 (7%)	5 (16%)
Planned birth control method			
None	6 (10%)	2 (7%)	4 (13%)
Abstinence	13 (22%)	3 (11%)	10 (32%)
Condoms	15 (25%)	7 (25%)	8 (26%)
Withdrawal	6 (10%)	2 (7%)	4 (13%)
Progesterone-only pills	5 (8%)	0 (0%)	5 (16%)
Combined oral	7 (12%)	3 (11%)	4 (13%)
Contraceptives	0 (0%)	0 (0%)	0 (0%)

Table 1 (continued)

	Total ($N = 59$)	Placebo arm ($N = 28$)	Estradiol arm ($N = 31$)
Vaginal ring	4 (7%)	2 (7%)	2 (6%)
Depo-Provera	10 (17%)	6 (21%)	4 (13%)
IUD	8 (14%)	7 (25%)	1 (3%)
Other			
Plan to breastfeed	56 (95%)	27 (96%)	29 (94%)

*At randomization; BMI = body mass index; GBS = group B streptococcus

Table 2 Primary and secondary outcomes overall and by treatment allocation

	Follow-up time	Entire cohort ($N = 59$)		Estrogen arm (B) ($N = 31$)		Placebo arm (A) ($N = 28$)		Mean difference* (Estrogen-placebo) (90% CI)
		N	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)	
Primary outcome								
VuAS (range = 0–3)	12 weeks	56	0.15 (0.24)	28	0.10 (0.25)	28	0.20 (0.22)	-0.10 (-0.20 to 0.01)
Secondary outcomes								
VuAS (range = 0–3)	6 weeks	56	0.76 (0.79)	29	0.73 (0.80)	27	0.79 (0.80)	-0.08 (-0.43 to 0.27)
	6 months	53	0.14 (0.27)	27	0.15 (0.27)	26	0.14 (0.27)	0.01 (-0.11 to 0.13)
VAS (range = 0–3)	6 weeks	33	0.33 (0.40)	18	0.28 (0.43)	15	0.39 (0.36)	-0.13 (-0.34 to 0.09)
	12 weeks	25	0.34 (0.39)	13	0.33 (0.43)	12	0.35 (0.36)	-0.03 (-0.30 to 0.23)
EPDS (range = 0–30)	6 weeks	55	4.71 (4.02)	28	4.68 (4.01)	27	4.74 (4.10)	-0.04 (-1.89 to 1.81)
	12 weeks	54	4.07 (3.34)	27	4.07 (3.71)	27	4.07 (2.99)	0.01 (-1.54 to 1.56)
	6 months	50	3.52 (3.75)	26	4.08 (3.86)	24	2.92 (3.62)	1.22 (-0.61 to 3.05)
UDI-6 (range = 0–100)	6 weeks	55	12.2 (21.5)	28	9.3 (11.3)	27	15.2 (28.4)	-5.73 (-15.51 to 4.05)
	12 weeks	54	8.0 (18.1)	27	5.6 (10.2)	27	10.5 (23.5)	-4.78 (-13.12 to 3.56)
	6 months	50	8.3 (15.4)	26	6.8 (13.0)	24	10.0 (17.8)	-2.58 (-10.11 to 4.95)
FISI (range = 0–61)	6 weeks	55	17.5 (12.5)	28	19.0 (11.9)	27	16.9 (13.2)	0.90 (-4.75 to 6.55)
	12 weeks	54	15.9 (13.3)	27	16.5 (14.3)	27	15.4 (12.4)	1.25 (-4.90 to 7.40)
	6 months	50	16.2 (14.1)	26	18.2 (14.9)	24	14.0 (13.1)	5.01 (-1.76 to 11.78)
FSFI (full scale range = 2–36)	6 weeks	51	12.5 (10.1)	27	13.3 (11.1)	24	11.7 (8.9)	1.59 (-3.23 to 6.41)
	12 weeks	53	22.9 (9.8)	26	25.4 (8.1)	27	20.5 (10.8)	5.11 (0.70 to 9.51)
	6 months	48	23.6 (9.0)	25	23.9 (8.8)	23	23.3 (9.5)	0.29 (-4.25 to 4.82)

*Mean difference is negative if adjusted estrogen arm scores are lower than placebo arm. Linear model is adjusted for laceration degree (2nd vs. 3rd/4th)

VuAS = Vulvar Assessment Scale; VAS = Vaginal Assessment Scale; EPDS = Edinburgh Postnatal Depression Scale; UDI-6 = Urinary Distress Inventory-6 ; FISI = Fecal Incontinence Severity Index; FSFI = Female Sexual Function Index

Table 3 Sensitivity analysis for primary outcome total and by treatment allocation*

		Total ($N = 53$)		Estradiol Arm ($N = 30$)		Placebo Arm ($N = 23$)		Mean difference Estrogen-placebo (90% CI)
VuAS (range 0–3)	6 weeks	51	0.78 (0.80)	28	0.75 (0.80)	23	0.81 (0.83)	-0.06 (-0.44 to 0.32)
	12 weeks	51	0.14 (0.24)	28	0.10 (0.25)	23	0.18 (0.23)	-0.09 (-0.20 to 0.03)
	6 months	48	0.13 (0.24)	27	0.15 (0.27)	21	0.10 (0.21)	0.05 (-0.07 to 0.17)

Values expressed as N, mean (SD)

VuAS = Vulvar Assessment Scale

*Excludes six treatment non-adherent patients; accounts for missing data in adherent patients

Table 4 Participant satisfaction, ease of use, and study drug adherence overall and by treatment allocation

	Total	Estradiol	Placebo arm
How satisfied are you with the product?			
Somewhat dissatisfied	1/54 (2%)	0/27 (0%)	1/27 (4%)
Neutral/unsure	19/54 (35%)	8/27 (30%)	11/27 (41%)
Somewhat satisfied	11/54 (20%)	5/27 (19%)	6/27 (22%)
Very satisfied	23/54 (43%)	14/27 (52%)	9/27 (33%)
How easy/difficult was the product to use?			
Neutral/unsure	6/54 (11%)	3/27 (11%)	3/27 (11%)
Easy	15/54 (28%)	5/27 (19%)	10/27 (37%)
Very easy	33/54 (61%)	19/27 (70%)	14/27 (52%)
Which term describes your perineum now compared with how it was before you began using the vaginal cream?			
No change	7/53 (13%)	1/27 (4%)	6/26 (23%)
A little better	6/53 (11%)	3/27 (11%)	3/26 (12%)
Much better	18/53 (34%)	9/27 (33%)	9/26 (35%)
Very much better	22/53 (42%)	14/27 (52%)	8/26 (31%)
How often did you use the medication 2 times per week?			
Not at all	2/53 (4%)	0/26 (0%)	2/27 (7%)
Some of the time	5/53 (9%)	1/26 (4%)	4/27 (15%)
About half of the time	3/53 (6%)	0/26 (0%)	3/27 (11%)
Most of the time	19/53 (36%)	10/26 (38%)	9/27 (33%)
All of the time	24/53 (45%)	15/26 (58%)	9/27 (33%)

half of participants (42.3%; 25/59) presented for a pelvic examination at 12 weeks. Most participants presenting for an examination had a vaginal pH level < 5 (60%; 15/25) and had vaginal findings within normal limits: normal moisture (80%; 20/25), good rugosity (92%; 23/25), normal thickness (92%; 22/24), normal epithelial integrity (92%; 23/25), good vascularity (92%; 22/24), and absent vaginal irritation (96%; 23/24). There were no notable differences by treatment allocation. Low rates of estrogen-based contraception were noted in the estradiol and placebo groups at 11% and 13%, respectively. Regarding the rate of return to intercourse for all queried participants, 26% reported resuming intercourse at 6 weeks, 80% at 12 weeks, and 84% at 6 months. Finally, there was one non-serious adverse event reported during the study, a urinary tract infection in the placebo arm deemed not related to study treatment.

Discussion

The results of this double-blinded placebo-controlled trial suggest a reduction in VuAS scores of 50% for the estrogen arm compared to the placebo (mean VuAS in placebo = 0.20 vs. estradiol = 0.10). However, this finding is interpreted with caution given the lower than expected VuAS scores in this cohort and early cessation of enrollment. Although the absolute reduction of the VuAS score is unlikely to have a clinically meaningful impact, women in the estradiol group were more likely to be satisfied with treatment.

The limited literature on vulvovaginal health of pre- and postpartum women highlights the need for descriptive studies as well as intervention studies in populations of women with a range of perineal symptoms. Our study used the VuAS tool to examine vulvar symptoms in a premenopausal population; the average score of 0.20 in the untreated population may be more consistent with postpartum patients compared to higher VuAS scores seen in postmenopausal patients or premenopausal patients with sexual dysfunction [22]. Most participants in our study (76%) reported lactation at 12 weeks postpartum while only 7% reported exclusively breastfeeding. Rates of breastfeeding vary widely both domestically and internationally [23]. As lactation has a significant role in the development of postpartum vulvovaginal atrophy, the generalizability of this study may be limited based on proportion of women breastfeeding in a certain population. While hypoestrogenemia has been described during lactation, the circulating estradiol levels of 30–40 pg/ml in breastfeeding women are higher compared to the approximately 18 pg/ml reported in postmenopausal women [3, 24]. These higher physiological estradiol levels may contribute to a lower prevalence of atrophy symptoms in the postpartum period compared to postmenopausal women leading to lower than expected baseline VuAS scores. The low rates of estrogen-based contraception likely did not contribute significantly to circulating estradiol levels in our study population.

Our study demonstrates similar postpartum sexual function scores and changes compared to prior studies [1, 25]. Specifically, our study found a mean FSFI full-scale score for the entire cohort at 6 weeks postpartum that was lower (12.5, SD 10.1) compared to the mean score at 12 weeks (22.9, SD 9.8) and 6 months (23.6, 9.0), trends that were noted to be similar across both treatment groups. Lower FSFI scores indicate a greater severity of dysfunction among sexually active women compared to higher scores, a trend that has been noted in early time points in the postpartum period compared to later time points [25].

Interestingly, FISI mean scores in our study were noted to be similar to scores seen in patients with anal sphincter injuries at our postpartum time points for the entire cohort at 6 weeks, 12 weeks, and 6 months: 17.5, 15.9, and 16.2, respectively. Leader-Cramer et al. noted a mean FISI score of 13.6 ± 12.5 at 1 week postpartum in a population of obstetric anal sphincter injuries [26]. In contrast, Borello-France et al. have described mean scores of 2.8 ± 5.2 at 6 weeks postpartum and 2.2 ± 4.9 at 6 months postpartum in primiparous women with and without anal sphincter tears. Higher FISI scores were noted in women with sphincter tears, 6.0 ± 8.1 at 6 weeks postpartum [27]. The difference in our FISI scores

compared to the current literature is unclear as our scores remained similarly elevated across all time points.

Study drug adherence rates during the study period were high in the estradiol group with 96% of patients indicating they used the medication "most" or "all of the time." Satisfaction rates were also favorable with the majority of patients in the estrogen group (52%) stating they were "very satisfied" at the end of the study period. The discontinuation rate among the entire cohort was 10.2% (five in the placebo arm, one in the estrogen arm) with one patient not starting the medication after randomization. Similar discontinuation rates are noted in randomized studies of vaginal estradiol and placebo in postmenopausal women of 4.2–9.8% at 12 weeks [28, 29]. During the short follow-up, vaginal estrogen for the management of postpartum vulvovaginal symptoms appeared safe and well tolerated. No serious adverse events were reported. While one patient in the placebo group reported a urinary tract infection, the event was not considered to be related to the study drug.

Strengths of this study include the double-blind randomized controlled trial study design, use of validated outcome measures, good adherence to study medication, and low attrition rate. Study medication compliance and attrition rates had been initial concerns in this postpartum cohort. We employed standardized and validated questionnaires as well objective physical assessments. Additionally, extensive delivery and clinical characteristics were collected to examine potential differences between treatment groups.

Limitations included early cessation of enrollment secondary to the COVID-19 pandemic and subsequent inability to reach our target sample size. Furthermore, while the VAS, VuAS, and FISI are objective measures of vaginal and vulvar health and sexual function, they have not been validated in a young postpartum population [22, 30]. Additionally, the racial and ethnic homogeneity of our population limits its generalizability of our findings. Finally, our treatment adherence data were limited. The study may have benefited from a loading dose at treatment initiation and the use of prospective medication diaries to limit bias. While there were no serious adverse events reports, larger studies with a heterogeneous population are needed to confirm safety.

Conclusions

This trial indicated a global presence of VVA symptoms in the postpartum period prompting further questions of its impact on quality of life and sexual function. The use of vaginal estradiol cream 1 g twice weekly may decrease vulvar atrophy symptoms in postpartum women, but the clinical benefit of these findings is likely minimal. This finding should be interpreted with caution given the small sample size in the estradiol compared to the placebo group. However, study findings support the acceptability, safety, and satisfaction up to 12 weeks postpartum related to local estrogen regardless of lactation practices. Larger adequately powered trials enrolling a diverse group of postpartum women are needed to further evaluate the efficacy of postpartum vaginal estrogen use.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00192-022-05149-x.

Authors' participation PE Smith: Project development, Data Collection, Manuscript writing

EM McLaughlin: Project development, Data Collection, Data analysis, Manuscript writing

LK Pandya: Project development, Data Collection, Manuscript writing

EM Hade: Project development, Data Collection, Data analysis, Manuscript writing

CD Lynch: Project development, Data Collection, Data analysis, Manuscript writing

CO Hudson: Project development, Data Collection, Manuscript writing

Declarations

Conflict of interest The study was sponsored by the 2017 Clinical Research Grant by the International Urogynecological Association and The Ohio State University Center for Clinical and Translational Science grant support (National Center for Advancing Translational Sciences, Grant UL1TR001070).

References

1. De Souza A, Dwyer PL, Charity M, Thomas E, Ferreira CHJ, Schierlitz L. The effects of mode delivery on postpartum sexual function: A prospective study. BJOG An Int J Obstet Gynaecol. 2015. https://doi.org/10.1111/1471-0528.13331.
2. Fairchild PS, Low LK, Kowalk KM, Kolenic GE, DeLancey JO, Fenner DE. Defining "normal recovery" of pelvic floor function and appearance in a high-risk vaginal delivery cohort. Int Urogynecol J. 2020. https://doi.org/10.1007/s00192-019-04152-z.
3. Agarwal SK, Kim J, Korst LM, Hughes CL. Application of the estrogen threshold hypothesis to the physiologic hypoestrogenemia of lactation. Breastfeed Med. 2015. https://doi.org/10.1089/bfm.2014.0030.
4. 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. https://doi.org/10.1097/01.AOG.0000296714.12226.0f.
5. Rahn DD, Carberry C, Sanses TV, et al. Vaginal estrogen for genitourinary syndrome of menopause. Obstet Gynecol. 2014. https://doi.org/10.1097/AOG.0000000000000526.
6. Rahn DD, Good MM, Shi H, Keller P, Roshanravan SM, Word A. Effects of preoperative local estrogen treatment on connective tissues of the vaginal wall in postmenopausal women with prolapse: a double-blind randomized controlled study. Female Pelvic Med Reconstr Surg. 2013.
7. Tennfjord MK, Hilde G, Stær-Jensen J, Ellström Engh M, Bø K. Dyspareunia and pelvic floor muscle function before and during pregnancy and after childbirth. Int Urogynecol J. 2014. https://doi.org/10.1007/s00192-014-2373-2.

8. Stær-Jensen J, Siafarikas F, Hilde G, Benth JS, BØ K, Engh ME. Postpartum recovery of levator hiatus and bladder neck mobility in relation to pregnancy. Obstet Gynecol. 2015. https://doi.org/10.1097/AOG.0000000000000645.
9. Wisniewski PM, Wilkinson EJ. Postpartum vaginal atrophy. Am J Obstet Gynecol. 1991. https://doi.org/10.1016/S0002-9378(12)90737-1.
10. Howard TF, Lewicky-Gaupp C. Postpartum vaginal agglutination: A case report. Female Pelvic Med Reconstr Surg. 2012. https://doi.org/10.1097/SPV.0b013e318253217a.
11. Kingsberg SA, Wysocki S, Magnus L, Krychman ML. Vulvar and vaginal atrophy in postmenopausal women: Findings from the REVIVE (REal women's VIews of treatment options for menopausal vaginal changEs) survey. J Sex Med. 2013. https://doi.org/10.1111/jsm.12190.
12. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019. https://doi.org/10.1016/j.jbi.2019.103208.
13. Carter J, Stabile C, Seidel B, Baser RE, Goldfarb S, Goldfrank DJ. Vaginal and sexual health treatment strategies within a female sexual medicine program for cancer patients and survivors. J Cancer Surviv. 2017. https://doi.org/10.1007/s11764-016-0585-9.
14. Carter J, Goldfarb S, Baser RE, et al. A Single-Arm Clinical Trial Investigating the Effectiveness of a Non-Hormonal Vaginal Moisturizer in Endometrial Cancer Survivors. Int J Radiat Oncol. 2019. https://doi.org/10.1016/j.ijrobp.2019.06.1764.
15. Carter J, Goldfarb S, Baser RE, et al. A single-arm clinical trial investigating the effectiveness of a non-hormonal, hyaluronic acid-based vaginal moisturizer in endometrial cancer survivors. Gynecol Oncol. 2020. https://doi.org/10.1016/j.ygyno.2020.05.025.
16. Carter J, Baser RE, Goldfrank DJ, et al. A single-arm, prospective trial investigating the effectiveness of a non-hormonal vaginal moisturizer containing hyaluronic acid in postmenopausal cancer survivors. Support Care Cancer. 2021. https://doi.org/10.1007/s00520-020-05472-3.
17. McCaffery M, Beebe A. Pain: Clinical manual for nursing practice. The Numeric Pain Rating Scale. Pain. 1989.
18. Cox JL, Holden JM, Sagovsky R. Detection of Postnatal Depression: Development of the 10-item Edinburgh Postnatal Depression scale. Br J Psychiatry. 1987. https://doi.org/10.1192/bjp.150.6.782
19. Shumaker SA, Wyman JF, Uebersax JS, McClish D, Fantl JA. Health-related quality of life measures for women with urinary incontinence: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Qual Life Res. 1994. https://doi.org/10.1007/BF00451721.
20. Rockwood TH, Church JM, Fleshman JW, et al. Patient and surgeon ranking of the severity of symptoms associated with fecal incontinence: The fecal incontinence severity index. Dis Colon Rectum. 1999. https://doi.org/10.1007/bf02236199.
21. Rosen R, Brown C, Heiman J, et al. The female sexual function index (Fsfi): A multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000. https://doi.org/10.1080/009262300278597.
22. Eaton AA, Baser RE, Seidel B, et al. Validation of Clinical Tools for Vaginal and Vulvar Symptom Assessment in Cancer Patients and Survivors. J Sex Med. 2017. https://doi.org/10.1016/j.jsxm.2016.11.317.
23. Zakarija-Grković I, Cattaneo A, Bettinelli ME, et al. Are our babies off to a healthy start? The state of implementation of the Global strategy for infant and young child feeding in Europe. Int Breastfeed J. 2020;15(1). https://doi.org/10.1186/s13006-020-00282-z.
24. Randolph JF, Zheng H, Sowers MFR, et al. Change in follicle-stimulating hormone and estradiol across the menopausal transition: Effect of age at the final menstrual period. J Clin Endocrinol Metab. 2011. https://doi.org/10.1210/jc.2010-1746.
25. Spaich S, Link G, Alvarez SO, et al. Influence of Peripartum Expectations, Mode of Delivery, and Perineal Injury on Women's Postpartum Sexuality. J Sex Med. 2020. https://doi.org/10.1016/j.jsxm.2020.04.383.
26. Leader-Cramer A, Kenton K, Davé B, Gossett DR, Mueller M, Lewicky-Gaupp C. Factors Associated With Timing of Return to Intercourse After Obstetric Anal Sphincter Injuries. J Sexual Med. 2016. https://doi.org/10.1016/j.jsxm.2016.07.010.
27. Borello-france D, Burgio KL, Richter HE. Fecal and Urinary Incontinence in. October. 2006.
28. Bachmann G, Bouchard C, Hoppe D, et al. Efficacy and safety of low-dose regimens of conjugated estrogens cream administered vaginally. Menopause. 2009. https://doi.org/10.1097/gme.0b013e3181a48c4e.
29. Freedman M, Kaunitz AM, Reape KZ, Hait H, Shu H. Twice-weekly synthetic conjugated estrogens vaginal cream for the treatment of vaginal atrophy. Menopause. 2009. https://doi.org/10.1097/gme.0b013e318199e734.
30. Cockell SJ, Oates-Johnson T, Gilmour DT, Vallis TM, Turnbull GK. Postpartum flatal and fecal incontinence quality-of-life scale: A disease- and population-specific measure. Qual Health Res. 2003. https://doi.org/10.1177/1049732303256410.