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OPTIMIZING POST-OPERATIVE HEALING FOLLOWING VAGINAL RECONSTRUCTIVE SURGERY: A TRIPLE ARM RANDOMIZED CLINICAL TRIAL OF AN ESTRADIOL-RELEASING VAGINAL RING

Hypothesis / aims of study
To evaluate the utility of early administration of vaginal estrogen via a continuous low dose estradiol vaginal ring immediately following pelvic reconstructive surgery

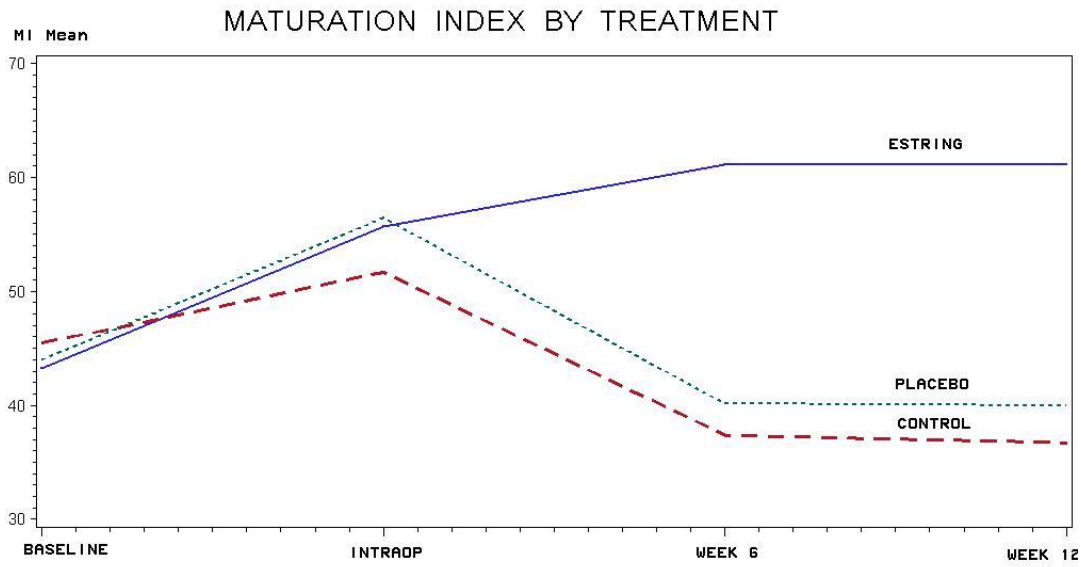
Study design, materials and methods
This was an IRB-approved randomized double blinded clinical trial on the early administration of estrogen via an estradiol-releasing intravaginal ring in women undergoing pelvic reconstructive surgery. 65 women with at least Stage II pelvic organ prolapse were randomly assigned to: estradiol-releasing vaginal ring (A), placebo vaginal ring (B), or control without vaginal ring (C). Inclusion criteria were postmenopausal women at least 2 years with symptoms and/or signs of urogenital atrophy and no use of vaginal estrogen in the past 6 months. Women with contraindications to estrogen use and allergies to silicone and/or estradiol were excluded from participation.
A standardized history and physical exam to assess urogenital atrophy and tissue quality were obtained at baseline and repeated at 6 and 12 weeks post-operatively. Patients and evaluators were blinded to their study group. The primary outcome was tissue quality based on vaginal maturation index. Secondary measures of tissue quality were vaginal pH, presence of granulation tissue, and microscopic evidence of inflammatory cells. Other measured outcomes were subjective and objective signs of atrophy and the ability to tolerate an intravaginal ring. Subjective atrophy symptoms (vaginal dryness, pruritis, dyspareunia, dysuria, and urinary urgency) and objective signs of atrophy (vaginal pallor, petechiae, friability, and dryness) were ranked on a scale of 0-4 (none-severe) to develop an overall subjective and objective score at each timepoint.
Repeated measures analysis was performed using generalized estimation equations methodology for interval and binary data. Chi square and ANOVA analysis were used as indicated.

Results
Twenty-two women had the estradiol-releasing vaginal ring; twenty the placebo vaginal ring; and twenty-two were controls without vaginal ring. Median age 65 (range 60-70), parity 2 (range 2-3), BMI 27 (range 24-30), years postmenopausal 17 (range 10-22) and prolapse stage 3 (range 2-3) were not different among the groups.
There was a statistically significant difference between the treatment arms for maturation index (MI) overall ($p=<0.01$) and across time ($p=<0.01$) (figure 1). At 12 weeks post-operatively, treatment group significantly correlated with MI ($p<0.01$) and treatment arms were significantly different with respect to MI (A 61.1 ± 12.3, B 36.7 ± 15.8, C 39.9 ± 13.8, $p<0.01$).
For vaginal pH, a statistically significant difference was seen overall ($p<0.01$) and across time ($p=0.05$) between the arms. At 12 weeks, treatment arms significantly correlated with pH ($p<0.01$) and were significantly different (A 5.30 ± 0.87, B 6.61 ± 0.71, C 5.97 ± 0.93, $p=0.03$).
Granulation tissue was significantly higher in the placebo ring group (B) at 12 weeks compared with groups A & C (A 1.3, B 5.6, C 1.1, $p<0.01$) but did not differ between the groups at 6 weeks. Presence of vaginal suture differed at 6 and 12 weeks ($p=0.03$) but did not differ based on treatment arm during the study period ($p=0.54$). No significant difference between the groups was seen for microscopic inflammatory cells at 6 and 12 weeks ($p=0.29$).
Subjective atrophy score at 6 and 12 weeks was not significantly different between the treatment groups ($p=0.39$) Overall objective atrophy assessment differed over time and was significantly lower for group A compared with groups B and C at 6 and 12 weeks [6 weeks A 1 (1-2.5), B 5 (3-7), C 5 (3-7) $p<0.01$; 12 weeks A 0 (0-0), B 5 (4-7.5), C 7 (3.5-7) $p<0.01$].
Overall 3 patients requested ring removal during the study period (1 group A 2, 2 group B), two rings “fell out” (1 group A, 1 group B), and one active ring was removed by the physician at 6 weeks due to severe vaginal inflammation. 6/22 in group A and 5/21 in group B requested continuation of the vaginal ring after the study period. Satisfaction rates did not differ among the groups ($p=0.42$).

Interpretation of results
Postoperative tissue quality as measured by vaginal maturation index, pH and objective atrophy assessment was enhanced in the treatment arm (group A) over the study time period. Granulation tissue was increased in the placebo arm (group B) at 12 weeks. Subjective atrophy scores did not differ within the treatment arms. The incidence of minor ring-related adverse events leading to study drop-out was acceptably low (6.2%, 4/65).

Concluding message
Early administration of vaginal estrogen following pelvic reconstructive surgery via an intravaginal ring is feasible, safe, and results in improved post-operative tissue quality.

Figure 1



Specify source of funding or grant	**None**
Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**No**
Is this a Randomised Controlled Trial (RCT)?	**Yes**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Institutional Review Board (Cleveland Clinic Florida) (IRB8940)**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**