Vaginal Estrogens

The research shows us that sometimes vaginal estrogen is not only safe, even with a history of breast cancer, but it is necessary for optimal vaginal health, especially for sexually active women whose vaginal function will deteriorate significantly without estrogen. When the ovaries fail to function either due to age or after breast cancer chemotherapy, vaginal estrogen can provide a lifeline of benefit to the vaginal and urethral walls without increasing the serum levels of estrogen over that of the menopausal women. This meets the needs of the Medical Oncologist to reduce estrogen delivery to the breast tissue, and helps the patient continue her normal relations with her spouse and avoid frequent urinary tract infections, urinary urgency, urinary frequency, urinary leakage and bleeding.1-4

In summary, it is essential that we oncologists use the evidence-based research to provide women the opportunity to have their vaginal lining supported by local estrogen as needed, by safely using doses that have been proven to not increase serum levels over menopausal levels.

Handa, V. L., K. E. Bachus, et al. (1994). "Vaginal administration of low-dose conjugated estrogens: systemic absorption and effects on the endometrium." *Obstet Gynecol* **84**(2): 215-8.
OBJECTIVE: To test the hypothesis tha a very-low-dose regimen of vaginal estrogen would provide effective relief from atrophic vaginitis without endometrial proliferation.
METHODS: Twenty postmenopausal women with symptoms, signs, and cytologic evidence of atrophic vaginitis were enrolled. Each subject was treated with 0.3 mg of conjugated estrogens, administered vaginally 3 nights per week for 6 months. We examined the following outcomes: symptoms, vaginal cellular (cytologic) maturity, endometrial histology, sonographic evaluation of endometrial thickness, Doppler measures of uterine artery blood flow, and serum levels of estrone and estradiol. Pre- and post-treatment data were compared for each subject.
RESULTS: Satisfactory relief of symptoms occurred in 19 of 20 cases. Vaginal cellular maturation improved significantly with therapy (P <01). **There were no significant changes in endometrial thickness, uterine artery blood flow, or serum estrogen levels.** Endometrial proliferation was observed in one case.
CONCLUSIONS: Relief from atrophic vaginitis can be achieved with 0.3 mg of conjugated estrogens administered vaginally two times per week. Endometrial proliferation may occur at this low dose, albeit rarely.

Notelovitz, M., S. Funk, et al. (2002). "Estradiol absorption from vaginal tablets in postmenopausal women." *Obstet Gynecol* **99**(4): 556-62.
OBJECTIVE: To evaluate absorption of estradiol (E2) and compare two low doses of 17 beta-E2 (25 microgram and 10 microgram) in postmenopausal women with atrophic vaginitis.
METHODS: In a double-masked, randomized, parallel-group study, 58 postmenopausal women were treated with 25 microgram or 10 microgram of 17 beta-E2 for 12 weeks. We report data for 42 eligible subjects who had serum E2 concentrations below 20 pg/mL at baseline and complete data available at the baseline visit (30 minutes before tablet insertion) and weeks 2 and 12. Serum E2 and FSH concentrations were measured at specified intervals. The area under the curve, maximal concentration, and time to maximal concentration were measured for serum E2 concentrations. Maturation values of vaginal epithelial cells were assessed as indicators of change in vaginal epithelium condition in response to treatment.
RESULTS: After 12 weeks of treatment, the area under the curve, maximal and average over 24-hour E2 concentration were higher in the 25-microgram (563 pg. hour/mL, 49 and 23 pg/mL) than in the 10-microgram (264 pg. hour/mL, 22 and 11 pg/mL) group. Seventy-four percent in the 25-microgram and 96% in the 10-microgram groups had low systemic absorption of E2, that is, area under the curve (0-24 hour) less than 500 pg/mL. **All but three women who received 25 microgram had mean FSH levels below 35 mIU/mL.**
CONCLUSION: Treatment with 25 or 10 microgram of 17 beta-E2 vaginal tablets resulted in low absorption of estrogen without systemic effects often associated with hormone replacement therapy. **After 12 weeks of therapy for atrophic vaginitis, absorption patterns remained consistent, and women did not have accumulations of circulating E2.**

Rioux, J. E., C. Devlin, et al. (2000). "17beta-estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis." *Menopause* **7**(3): 156-61.
OBJECTIVES: The efficacy and safety of 25-microg 17beta-estradiol vaginal tablets (Vagifem) were assessed and compared with 1.25-mg conjugated equine estrogen vaginal cream (Premarin Vaginal Cream) for the relief of menopausal-derived atrophic vaginitis, resulting from estrogen deficiency.
DESIGN: In a multicenter, open-label, randomized, parallel-group study, 159 menopausal women were treated for 24 weeks with either vaginal tablets or vaginal cream. Efficacy was evaluated by relief of vaginal symptoms and concentrations of serum estradiol and follicle-stimulating hormone. Safety was monitored by the incidence of adverse events, evaluation of endometrial biopsies, and clinical laboratory results. Patients also assessed the acceptability of the study medications.
RESULTS: Composite scores of vaginal symptoms (dryness, soreness, and irritation) demonstrated that both treatments provided equivalent relief of the symptoms of atrophic vaginitis. At weeks 2, 12, and 24, increases in serum estradiol concentrations and suppression of follicle-stimulating hormone were observed in significantly more patients who were using the vaginal cream than in those who were using the vaginal tablets ($p < 0.001$). Fewer patients who were using the vaginal tablets experienced endometrial proliferation or hyperplasia compared with patients who were using the vaginal cream. Significantly more patients who were using the vaginal tablets rated their medication favorably than did patients who were using the vaginal cream ($p <$ or $= 0.001$). Patients who were receiving the vaginal tablets also had a lower incidence of patient withdrawal (10% versus 32%).
CONCLUSIONS: Treatment regimens with 25-microg 17beta-estradiol vaginal tablets and with 1.25-mg conjugated equine estrogen vaginal cream were equivalent in relieving symptoms of atrophic vaginitis. **The vaginal tablets demonstrated a localized effect without appreciable systemic estradiol increases or estrogenic side effects.** Vaginal tablet therapy resulted in greater patient acceptance and lower withdrawal rates compared with vaginal cream therapy.

Simunic, V., I. Banovic, et al. (2003). "Local estrogen treatment in patients with urogenital symptoms." *Int J Gynaecol Obstet* **82**(2): 187-97.
OBJECTIVES: Determination of the efficacy and safety of vaginally administered low dose (25 microg) micronized 17beta-estradiol in the management of patients with urogenital symptoms.
METHODS: A total of 1612 patients with urogenital complaints were randomized to receive 25 microg of micronized 17beta-estradiol (n=828) or placebo (n=784) in a multicenter double-blind placebo-controlled study running for 12 months. Female patients were treated once a day over a period of 2 weeks, and then twice a week for the remaining of the 12 months with an active or placebo tablet. The assessment included full history-questionnaire, micturition diary, gynecologic and cystometric examination, transvaginal ultrasound, and serum 17beta-estradiol level determination. It was carried out at the beginning, and after 4 and 12 months of treatment.
RESULTS: The overall success rate of micronized 17beta-estradiol and placebo on subjective and objective symptoms of postmenopausal women with vaginal atrophy was 85.5%, and 41.4%, respectively. A significant improvement of urinary atrophy symptoms was determined in vaginal ERT group as compared with the beginning of the study (51.9% vs. 15.5%, P=0.001). **The maximal cystometric capacity (290 ml vs. 200 ml, P=0.023), the volume of the urinary bladder at which patients first felt urgency (180 vs. 140, P=0.048), and strong desire to void (170 ml vs. 130 ml, P=0.045) were significantly increased subsequent to the micronized 17beta-estradiol treatment. The number of patients with uninhibited bladder contractions significantly decreased following micronized 17beta-estradiol as compared with pretreatment values (17/30, P=0.013).** Side effects were observed in 61 (7.8%) patients treated with low dose micronized 17beta-estradiol. **Therapy with 25 microg of micronized 17beta-estradiol did not raise serum estrogen level nor stimulated endometrial growth.**
CONCLUSIONS: Local administration of 25 microg of micronized 17beta-estradiol is an effective and a safe treatment option in the management of women with urogenital complaints.

Ballagh SA. Vaginal rings for menopausal symptom relief. *Drugs Aging*. 2004;21(12):757-766.
The vagina is an alternative delivery site of sex steroids for menopausal women. New ring technology provides continuous and consistent delivery of steroids for up to 3 months. Rings rest on the pelvic floor muscles in a nearly horizontal position and are usually imperceptible. Steroid is delivered directly into the systemic circulation which may result in less alteration of coagulation/fibrinolysis pathways as seen with

transdermal hormone therapy. Fewer adverse effects are noted when progesterone is applied vaginally, possibly due to lower serum levels of metabolites such as alloprenanolone. Women often switch to a ring for the longer dosing interval but also appreciate the reduced messiness. Over 5700 healthy US women who evaluated an unmedicated ring as a drug delivery platform found it very acceptable independent of age or prior use of barrier contraceptives. Marketed rings in the US include: (i) a ring for systemic and vaginal menopausal therapy that provides average serum estradiol levels of 40.6 pg/mL for the 0.05 mg and 76 pg/mL for the 0.1 mg dose; (ii) **a ring for urogenital menopausal symptoms only that minimally elevates serum estradiol, usually within the menopausal range, treating atrophic vaginitis and urethritis; and** (iii) a ring labelled for contraception that provides ethinyl estradiol 15 microg and etonogestrel 120 microg appropriate for nonsmoking perimenopausal women. A ring for combination hormone therapy and another releasing progesterone for contraception in lactating women have been reported in the literature, but are not yet available commercially. These may offer future options for hormone therapy. Women with a uterus receiving estrogen, even in low doses, should be given progestogen to prevent endometrial hyperplasia or carcinoma. Even women who have had an endometrial ablation are likely to have some endometrial tissue remaining since long-term amenorrhoea is uncommon. Since no marketed combination ring product is available, other forms of progestogen are necessary. Vaginal rings offer a novel approach to menopausal hormone therapy producing consistent serum levels sustained for up to 3 months per unit dose with lower adverse effects than other vaginal products and high acceptability among users.

Park K, Ahn K, Lee S, Ryu S, Park Y, Azadzoi KM. Decreased circulating levels of estrogen alter vaginal and clitoral blood flow and structure in the rabbit. *Int J Impot Res*. May 2001;13(2):116-124.
Aging and menopause related decline in circulating levels of estrogen has been shown to adversely affect female sexual arousal function. Our aim was to study the effects of circulating levels of estrogen on the hemodynamic mechanism of vaginal and clitoral engorgement and on the structure of the vaginal and clitoral cavernosal tissue in the rabbit. New Zealand White female rabbits (3.5-4 kg) were randomly divided into three groups with five rabbits in each group: control; bilateral oophorectomy; bilateral oophorectomy undergoing subcutaneous injection of estrogen (40 microg/kg/day). After 6 weeks, the serum levels of 17 beta-estradiol were measured and systemic blood pressure was monitored. Vaginal and clitoral cavernosal blood flows were measured with laser Doppler flowmeter before and after pelvic nerve stimulation. Cross sections of the clitoris and vagina were processed for histologic examination and histomorphometric image analysis. Serum level of 17 beta-estradiol (pg/ml; mean+/-s.d.) revealed a significant decrease in the oophorectomy group (25.4+/-5.1) compared with the control (38.5+/-7.6) and estrogen replacement (115.9+/-57.3) groups (P<.05). **Nerve stimulation-induced peak vaginal and clitoral intracavernosal blood flows in the oophorectomy group (28.9+/-16.3 and 6.1+/-1.4, respectively) were significantly less than those recorded in the control (48.9+/-6.5 and 11.0+/-2.4, respectively) or estrogen replacement (48.7+/-12.2 and 10.1+/-2.8, respectively) group (P<.05). In histology, marked thinning of the vaginal epithelial layers, decreased vaginal submucosal microvasculature, and diffuse clitoral cavernosal fibrosis were evident in the oophorectomy group but not in the estrogen supplement and control groups.** In histomorphometry, the percentage of clitoral cavernosal smooth muscle in the oophorectomy group (49.6+/-6.2) was significantly decreased compared with the control (56.8+/-2.6) and estrogen replacement (58+/-3.0) groups (P<.05). Our studies show that decline in circulating levels of estrogen impairs the hemodynamic mechanism of vaginal and clitoral engorgement and leads to histopathologic changes in the vagina and clitoral cavernosal tissue. These observations suggest that decreased circulating levels of estrogen, a physiologic change in the menopausal state, may play a role in the development of female sexual arousal dysfunction.

Taechakraichana N, Intraragsakul A, Panyakhamlerd K, Numchaisrika P, Limpaphayom K. Estradiol and follicle-stimulating hormone levels in oophorectomized women using vaginal estrogen. *J Med Assoc Thai*. Nov 1997;80(10):626-630.
To assess the changing estradiol (E2) and follicle-stimulating hormone (FSH) level in oophorectomized women using vaginal estrogen. Serum estradiol and FSH were evaluated in 32 oophorectomized women using a daily dose of 2 g base of 1.25 mg vaginal conjugated equine estrogen (CEE) cream. The blood sample for hormone assay was collected 8-10 hours from the time of vaginal application. E2 and FSH levels were measured in the serum sample before and after commencing the study at 4, 8 and 12 weeks using the time-resolved fluoroimmunoassay method. Serum estradiol significantly increased from baseline

value at 4, 8 and 12 weeks. (Mean +/- SD of E2 value at 0, 4, 8, 12 weeks: 9.97 +/- 12.13, 249.83 +/- 170.46, 299.38 +/- 190.65, 322.82 +/- 218.31 pmol/L, respectively, $P < 0.05$) On the other hand, serum FSH significantly decreased from baseline value at 4, 8 and 12 weeks. (Mean +/- SD of FSH value at 0, 4, 8, 12 weeks: 77.64 +/- 27.24, 40.33 +/- 21.64, 38.84 +/- 22.33, 30.90 +/- 24.32 IU/L, respectively, $P < 0.05$) In conclusion, a daily dose of 2 g vaginal CEE cream raised the serum estradiol level close to the normal level in the follicular phase of the normal menstrual cycle. However, even though FSH significantly decreased it did not reach the premenopausal level.

Handa VL, Bachus KE, Johnston WW, Robboy SJ, Hammond CB. Vaginal administration of low-dose conjugated estrogens: systemic absorption and effects on the endometrium. *Obstet Gynecol*. Aug 1994;84(2):215-218.

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