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Local Effects of Vaginally Administered Estrogen Therapy: A Review

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Abstract

The results of the Women's Health Initiative (WHI) led to a distinct decline in the routine use of estrogen as preventive therapy for vasomotor symptoms, osteoporosis, and cardiovascular disease in postmenopausal women. Without estrogen replacement, one third of women experience symptoms of atrophic vaginitis including dryness, irritation, itching and or dyspareunia. Local application of estrogen has been shown to relieve these symptoms and improve quality of life for these women. In addition, local estrogen therapy may have a favorable effect on sexuality, urinary tract infections, vaginal surgery, and incontinence. This review examines the effects of vaginally applied estrogen on the vaginal epithelium, urethra and endometrium. An accompanying review examines the systemic effects of vaginally applied estrogen.

Keywords

vaginal estrogen; vaginal atrophy; menopause; quality of life

Introduction

Following publication of the results of the Women's Health Initiative (WHI) trial, most women are no longer routinely placed on estrogen replacement as a preventive therapy. Without estrogen replacement, the vaginal epithelium and underlying connective tissue can thin, and for a third of women, this results in dryness, discomfort, itching, and/or painful intercourse, often referred to as atrophic vaginitis. Transvaginal estrogen is generally used to help postmenopausal women specifically with vaginal and lower urinary tract symptoms such as dryness and dyspareunia, urgency and frequency, as well as urinary tract infections.[1,2] Furthermore, gynecologic surgeons often pre-treat vaginal atrophy prior to performing surgery for pelvic floor disorders such as incontinence and prolapse. The purpose of this report is to review the impact of various forms of transvaginal estrogen on the urogenital tract (vagina, endometrium and bladder). Systemic effects are detailed in the companion review to this article.[3]

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The Vagina as Drug Delivery System

In 1918 Macht demonstrated that the vagina was able to absorb drugs including morphine and atropine. While drugs administered vaginally are often used to treat local conditions, these drugs may also act systemically.[4] Some oral agents are commonly used vaginally for non-FDA indications such as misoprostol for labor induction. Oxybutynin was initially marketed as an oral formulation and now is available in a vaginal ring for treatment of overactive bladder. The use of the vagina as a drug delivery system will most likely continue to increase because of the many qualities that make it suitable for absorption of drugs. Oral administration of drugs may be complicated by vomiting, variations in GI absorption, and drug interactions. Similarly, transdermal application is susceptible to variable outcomes based on levels of adiposity. One of the major advantages of vaginally administered drugs is avoidance of "hepatic first pass effect", which affects the absorption, distribution and excretion of orally administered drugs. This results in use of lower doses to achieve equivalent therapeutic effect.[4] Also, patients may benefit from less frequent dosing which decreases fluctuations in drug levels and can result in fewer side effects.[4]

One concern many patients have about vaginally applied medications is that it will "fall out."[4] However, the proximal vagina is relatively horizontal in the upright female and the vaginal rugae provide adequate surface area for drug absorption. In addition, innervation of the vagina is mainly concentrated in the distal portion, while the horizontally positioned proximal portion is mostly devoid of sensory endings, making drug application more comfortable. Finally, the vagina is a highly vascular organ, resulting in a ready epithelial/vascular interface for absorption. One interesting result of the large blood supply surrounding the vagina is the "first uterine pass effect" which results in higher uterine levels of a vaginally applied drug compared to systemic administration.[4,5] Another advantage is the discreet nature of vaginal administration. One of the few disadvantages of vaginally administered medications is overcoming patients' initial reluctance to use this method of administration due to misinformation.[4]

Based on the patient's preference, there are multiple options for vaginal hormone delivery. Two vaginal creams are available: one with estradiol (Estrace®, 0.1 mg estradiol/gm cream) and one with conjugated equine estrogens (Premarin®, 0.625 mg CEE/gm cream). There is also a vaginal tablet with (Vagifem®), 25.8μg of estradiolhemihydrate equivalent to 25 μg of estradiol. In addition there are vaginal rings: Femring® with available doses of either 50 μg/day or 100 μg/day, Estring® with 7.5 μg/day, and a combined estradiol/progesterone ring, which is not currently available commercially in the US.

Local Vaginal Effects

Notelovitz et al.[6] examined the local vaginal effects of vaginal tablets at two different doses: 10 and 25 μg. Participants were treated for a total of 12 weeks. The results of the treatment on vaginal maturation was measured by the vaginal maturation index (VMI), a surrogate measure of vaginal atrophy which measures estrogenic effect by examining the percentage of superficial cells which are mature epithelial cells with small nuclei due to an estrogenic effect. The study showed significant improvement after 12 weeks of treatment, where 60% of subjects in each treatment group had increased maturation values. A relationship between increased maturation values and serum E_2 levels, however could not be demonstrated.[6]

The effects of vaginal rings containing estradiol on the vaginal epithelium have also been studied. In a study of Femring®, the number of superficial cells increased by 16% and 18% with 50 μg and 100 μg, respectively, of estradiol, in comparison to 1.11% increase with placebo. Vaginal pH decreased with use of Femring® by 0.73 and 0.6 pH units for 50 μg and 100 μg respectively, with placebo use resulting in a 0.25 pH unit decrease.[7]

Femring® was studied in postmenopausal women by Speroff for the United States Vaginal Ring (VR**)** Investigational Group (2003).[8] With both doses studied, the mean change in the maturation index of vaginal cells from baseline to final evaluation was significantly greater for both doses than placebo. After completion of the study, no women on the 50 μg/day dose and only one woman on 100 μg/day (5%) had vaginal atrophy while 6 women (15%) on placebo continued to exhibit vaginal atrophy.[8]

Estring® is a vaginal ring containing 2 mg of estradiol released at a rate of 7.5 μg/day for 90 days. The use of the Estring® was compared to conjugated estrogen vaginal cream and no difference was noted in efficacy or improvement of vaginal dryness and atrophy both from a physicians' and patients' assessment. In one study, Estring® showed an 83% improvement compared to 82% for the vaginal cream, while another study showed Estring® improved symptoms in 79% versus 75% for the cream.[9]

Estring® had similar efficacy to conjugated estrogen vaginal cream in its ability to decrease pH as well as promote vaginal cell maturity.[9] Furthermore, the use of the Estring® resulted in no cases of endometrial hyperstimulation as compared to conjugated estrogen cream where 11% of participants had resulting endometrial overstimulation.[9] Estring® also exceeded vaginal cream in comfort as judged by patients with Estring® being rated as excellent or very good comfort for 95% compared to 65% for the cream. Ease of use for Estring® was judged excellent or very good in 95% compared to 88% for the vaginal cream.[9]

Vaginal Estrogen: Urinary Tract Infections and Lower Urinary Tract Symptoms

Urinary Tract Infections

In a study by Eriksen,[10] postmenopausal women who experienced greater than 3 urinary tract infections in the prior year were treated with Estring® to test prevention of recurrence compared to placebo. Estring® was shown to result in a significantly higher cumulative proportion of participants without recurrent urinary tract infections compared to placebo. After thirty-six weeks, 45% of participants on Estring® did not have a recurrence compared to 20% of those on placebo (P=0.008) (Fig 1). In addition, Estring® resulted in a significant decrease in vaginal pH by 12 weeks of therapy. Vaginal and urethral epithelium were more mature based on cytologic findings as determined by examination of the number of parabasal cells, intermediate cells and superficial cells in vaginal and urethral smears.[10]

Bladder Storage Symptoms and Urinary Incontinence

The decrease in ovarian estrogen production at the time of menopause causes atrophic changes in the vulvar, vaginal, urethral and bladder tissue. While vasomotor symptoms may resolve in a few months or years, vaginal and other urogenital symptoms may actually increase as the patient ages. [11] The effects of estrogen are manifest by the presence of Estrogen Receptors (ERs). Estrogen receptors have been shown in biopsy specimens from the bladder trigone, proximal urethra, distal urethra, vagina and vesico-vaginal connective tissue contiguous with the bladder neck.[12, 13,14] While ERs were present in urethral squamous epithelium, they were not present in urothelial tissue of the lower urinary tract. Progesterone receptors are more variable and found mostly in subepithelial tissues.

Decreased estrogen levels after menopause causes atrophic urogenital symptoms with several recent studies confirming resultant dysuria and other lower urinary tract symptoms such as urgency and frequency. Iosif studied a cohort of Swedish women and found a 50% incidence of urogenital symptoms including dryness, itching, burning, urgency and

frequency.[15] Barlow reported that 23-40% of menopausal women report at least one urogenital symptom.[16] In a 1954 paper, Youngblood [17] reported that symptoms of urgency and irritation were due to “atrophic urethritis” which is defined at symptoms of UTI without a positive culture.

Another study examined the effects of vaginal hormonal therapy on the urinary tract of postmenopausal women post hysterectomy by evaluating the blood flow at the urethral neck after either 0.625 mg oral or vaginal conjugated estrogen cream.[18] The urethral vascular network contributes significantly to urethral epithelial coaptation pressure which may influence some types of urinary incontinence. One measurement of blood flow is the pulsatility index; the greater the blood flow, the lower the pulsatility index. Treatment with both oral and vaginal estrogen resulted in significantly lower pulsatility index compared to baseline.[18] Additionally, there was a significant increase in the number of periurethral vessels with both treatment options. Symptoms of urinary frequency and nocturia showed a significant decrease for both oral and topical treatment after three months. While there was no significant change in the prevalence of stress and urge incontinence as measured by urodynamic studies, subjective symptom improvement of stress incontinence was reported in 72.7% of participants using oral replacement compared to 60% in the topical estrogen group.[18] A sub-study of the WHI showed an increase in stress urinary incontinence in postmenopausal women after oral estrogen/progestin therapy, but in women under the age of 60 there was no significant increase.[19] In contrast, the Hormone and Urogenital Therapy Committee reviewed 35 articles on stress incontinence which showed a subjective improvement in stress incontinence ranging from 64-75% with intravaginal and/or oral estrogen therapy.[20] Currently, the role of intravaginal estrogen in the treatment of stress incontinence is not clear.

Local estrogen therapy has been shown to increase urethral closing pressure with improvement of urge incontinence symptoms.[21] The women who experienced relief were found to have concurrent squamous metaplasia of the lower urethral transitional epithelium. In addition, uninhibited bladder contractions were noted to decrease in those using vaginal estrogen.[21] The apparent paradox of improvement in stress and urgency symptoms with local estrogen in some studies, and lack of improvement in stress incontinence symptoms as noted in the HERS study [22] may be partially explained if one assumes that the major effect of local estrogen is to improve urethral epithelium and coaptation without affecting the anatomic urethral supporting mechanisms. Further evidence for a direct effect of local estrogen on the urethral epithelium was provided by Bhatia who showed that menopausal women utilizing intravaginal estrogen demonstrated more mature/superficial epithelial components in urethral swabs compared to untreated women.[21] These women were also noted to have fewer symptoms of atrophic urethritis than controls.

It is difficult to perform studies of relief of vaginal and urinary symptoms since both have been reported to improve without active intervention and with application of non medicated lubricants and placebo creams.[23,20] Herbal therapy had not been shown to improve symptoms[24] and vaginal lubricants are less effective than estrogens.[25]

The issue of nocturia has been addressed in a recent Cochrane review which examined a variety of estrogen therapies and found no difference in frequency, nocturia or urgency.[26] In addition, Lose[27] studied 251 women treated with either an oestradiol releasing ring or oestradiol pessaries for 24 weeks. Subjective scores for urgency, frequency, nocturia, dysuria, stress incontinence, and urge incontinence were examined. Fifty one percent of the patients treated with the ring had improvement in nocturia versus 54% with the pessary. Sixty percent of patients rated the ring as excellent versus 14% for the pessaries. There was no placebo group in this trial. Finally, Simunic et al studied the effects of intravaginal

estrogen in patients with urogenital symptoms using 25 μg of 17ß estradiol or placebo for 12 months. After 12 months of therapy, urinary atrophy symptoms defined as complaints of dysuria, frequency, or urinary incontinence or greater than two UTIs in the past year were present in 35.9% of patients treated with placebo versus only 15.5% of patients treated with estradiol.[28] Nocturia and frequency was reduced from 32.8% in patients treated with placebo to 9.4% in the estradiol group. In this study, it appears that intravaginal estrogen has a favorable effect on both vaginal irritative symptoms as well as urinary incontinence.

Estring® has also shown improvement in symptoms of dysuria and urinary urgency. In a US study conducted by the manufacturer, symptoms of dysuria and urinary urgency improved in 74% and 65% of patients receiving Estring® as assessed by the patients only. In a companion Australian study, symptoms of dysuria and urinary urgency improved in 90% and 71% respectively, of patients receiving Estring®, again assessed by the patients in the study population.

Vaginal Estrogen and Sexual Function

It is well established that estrogen deficiency occurring at and beyond menopause may disrupt many of the physiological responses which characterize sexual arousal, including smooth muscle relaxation, vasocongestion and vaginal lubrication.[29] The decreased lubrication and tissue elasticity in addition to shortening of the vaginal vault can cause dyspareunia.[29] In addition, decreased sensory response and patient reaction to her social situation, loss of a long-term partner, changes in body image, and medication may cause undesired alterations in sexual habits. Other factors which may contribute to decreased sexual function include length of relationships, aging, physical and mental health problems, loss of partner's health, medication use, and other financial and social stressors.[30] The intent of this section is to address only those changes that may be affected by use of various forms of vaginal estrogen administration.

There is a strong correlation between serum levels of estradiol, vaginal atrophy and subsequent dyspareunia. Although both estradiol and estrone production decreases following menopause, estrone becomes the predominant estrogen in the postmenopausal period. While there is little change in testosterone levels associated with menopause, testosterone levels decrease with age because of decreased adrenal androgen synthesis.[31, 32] Ovarian stromal cells continue to produce pre-androgen and testosterone.[33] Therefore, in the postmenopausal woman, estrogen is produced extragonadally from ovarian and adrenal androgens.[30] Women whose estradiol levels are > 50 pg/ml have been shown to have less vaginal dryness and dyspareunia during sexual activity. In addition, decreased coital activity is associated with estradiol levels < 35 pg/ml.[29,34] As previously noted in this review and elsewhere, topical estrogen can improve vaginal lubrication and reduce dryness and dysparunia.[34,35,36] In addition, it has been shown that relief of these symptoms may increased quality of life, arousal and orgasmic function.[37,38]

Bachmann, and others [38,39] noted that restoring vaginal epithelial health with estrogen results in increased vaginal compliance,[39]decreased vaginal pH, increased vaginal blood flow and lubrication.[34] Changes in vaginal fluids and electrolytes have been noted with one month of therapy[40] and in pH, blood flow and vaginal electropotential in 18-24 months.[40] Women subsequently report decreased vaginal irritation, pain, dryness[42] and burning during intercourse,[42,41] which may lead to increased sexual desire,[34] arousal [40,43] and improved quality of life.[42]

Multiple studies have examined the effects of oral and transdermal estrogen on sexual function. However, few studies have evaluated the effects of vaginal estrogen alone for improvement in sexual function. Gast, et al enrolled 285 healthy sexually active post

menopausal women aged 45-65 years in a study of oral low dose conjugated estrogen (CEE) 0.45 mg/medroxyprogesterone 1.5mg for six, 28 day cycles along with 1 gm CEE (0.625mg) vaginal cream for the first six weeks of the trial versus a placebo cream and tablet.[44] The efficacy of the regimens was assessed by the McCoy Female Sexuality Questionnaire, self reported daily diary cards, the Brief Index of Sexual Functioning -Women (BISF-W) and the Women's Health Questionnaire. The author found that the estrogen therapy (ET) group had a significant decrease in frequency of dyspareunia compared to placebo and baseline by the McCoy Female Sexuality Questionnaire. ET was also associated with improvement in the level of sexual interest, frequency of orgasm, and pleasure of orgasm. However, there was no effect on coital frequency in this study. In another study, Cayan reviewed 169 women who received either oral 17β E_2 (Hormone Therapy, HT), 17βE_2 plus drosperinone, oral tibilone or vaginal 17β estradiol alone. [45] Sexual function was evaluated with a 19-item questionnaire, the Sexual Function Index, including evaluation of sexual desire, arousal, lubrication, orgasm, satisfaction and pain. In the women studied, the sexual function score increased in the hormone therapy (HT) group and decreased in the control group. The best improvement in total score and arousal was in the hormone therapy group while the highest improvement in lubrication was in the oral and vaginal 17ß estradiol group. Likewise, the best improvement in pain was in the oral and vaginal 17β estradiol groups. However, the vaginal therapy only group did not have a favorable response in desire, arousal, orgasm or satisfaction compared to the oral 17β E_2 group.[45]

Vaginal Estrogen and Surgery

It is commonly believed and anecdotal experience would predict that a well-estrogenized vagina heals better and is more resistant to complications such as infections and mesh erosions than more poorly estrogenized tissue. Many expert gynecologic surgeons recommend both pre- and postoperative vaginal estrogen for postmenopausal patients. However, there are few studies available which directly address the issue of vaginal estrogen on perioperative outcome.

It is known that topical estrogen can treat age-related skin changes such as wrinkles and thin skin.[46] Estrogen also increases the rate of cutaneous wound healing in older women and men. Estrogens act on the cutaneous wound healing response by modulating the inflammatory response, cytokine expression and matrix deposition. They also accelerate re-epithelialization, stimulating angiogenesis and wound contraction, and regulate proteolysis.[46] While estrogens' impact wound on healing of nonkeratinized vaginal epithelium remains to be described, its potential positive impact, currently adds to the rationale for perioperative use in vaginal surgery. There are no studies that directly compare the ease of the surgical procedure or its outcomes in women pretreated with intravaginal estrogen compared to those without treatment with intravaginal estrogen.

Vaginal Estrogen and the Endometrium

Intravaginal application of estrogen plays a unique role in hormone replacement therapy because of evidence that there is preferential delivery of hormones supplied in the vagina to the endometrium. This has been termed the "first uterine pass effect." This phenomenon is theorized to be the result of countercurrent exchanges with vein to artery diffusion. While this phenomenon is known to occur in the upper third of the vagina; it was unclear if this occurs throughout the vagina. A recent study examined this phenomenon. Vagifem® was applied in postmenopausal women either in the lower or upper third of the vagina. Estradiol levels along with Doppler velocity measurements were made both at baseline and after 2 hours. Application to the upper third of the vagina resulted in statistically significant higher serum estradiol levels but only a small absolute difference compared to the lower third of the

vagina. Also, with application of Vagifem® to the upper third of the vagina, there was a decrease in pulsatility index and resistance index which was not seen with lower third application. Thus, the first pass uterine effect appears to be exclusive to the upper third of the vagina. With application to the lower third of the vagina there was preferential delivery to the periurethral area.[47]

One major concern of unopposed long-term intravaginal estrogen therapy is the effect on the endometrium. One component of the Postmenopausal Estrogen/Progestin Interventions Trial examined the effects of oral estrogen alone compared to oral estrogen plus progesterone and placebo. Oral conjugated estrogens administered without concomitant progestin increased various forms of hyperplasia, 27% of cases resulting in simple hyperplasia compared to 8% with placebo. Hyperplasia rates in patients who received progesterone were similar to placebo. The subsequent addition of progestin after unopposed estrogen treatment resulted in hyperplasia reverting to normal in 94% of cases.[48]

In a study of 159 patients, Vagifem® tablets given daily for 2 weeks, then twice weekly, were compared to CEE vaginal cream 1.25 mg for 3-week cycles over 6 months. There was similar improvement in symptoms of vaginal dryness, soreness, and irritation in both the Vagifem® and comparator group. No statistical differences were found on endometrial biopsies that were performed to assess the presence of endometrial hyperplasia or malignancy with Vagifem use. Similar rates of endometrial atrophy were noted in the Vagifem® and placebo group (84%and 86% respectively). There was one patient whose biopsy showed simple hyperplasia in the Vagifem® group (3%) vs none in the placebo group. No patients in either group showed complex hyperplasia or malignancy.[49] Another arm of the study compared endometrial biopsy data of patients treated with Vagifem® to CEE over 24 weeks. Thirty-four (68%) of the Vagifem® group vs 15 (30%) of the CEE group showed atrophy, 2% vs 14% weakly proliferative endometrium, 0% vs 2% simple hyperplasia, and 0% vs 2% complex hyperplasia. Insufficient tissue was noted in 28% vs 42% of Vagifem®- and CEE- treated patients, respectively.

Weisberg et al examined the results of 48 weeks of use of Estring® and Vagifem® on vaginal symptoms including vaginal dryness, puritis, dyspareunia, and endometrial changes associated with menopause. There was no change in endometrial thickness over the first 12 weeks of observation for either group. Bleeding occurred in 4 patients using Vagifem® while no patients had bleeding with Estring®.[50] Another assessment of endometrial response was performed by Naessen and Rodriguez-Macias.[51] They compared 12 months of Estring® use to placebo. Endometrial thickness did not increase with prolonged use of Estring®. Baseline endometrial diameter was 2.8 mm and at the conclusion of the study 12 months later was 2.6 mm. Endometrial thickness was noted to be associated with waist circumference, body mass index (BMI), and estradiol levels.[51]

A study by Maruo et al.[52] posed the question: does the addition of progesterone to estradiol in vaginal rings prevent endometrial proliferation in postmenopausal women? Two doses of progesterone were tested: approximately 5 mg/day and 9 mg/day, combined with estradiol released at approximately 150 μg/day. Serum estradiol levels reached a peak level of 69 pg/ml at 2 weeks and decreased to 36 pg/ml at 6 months. Estrone levels remained stable at a mean level of 94 pg/ml. The high dose progesterone studied reached a peak serum level of 4.8 ng/ml at 2 weeks and then decreased to 2.6 ng/ml at 6 months. Similarly, the low dose progesterone reached a maximum serum concentration of 2.8 ng/ml and decreased to 1.4 ng/ml. (Fig 1) Biopsies were obtained at 4 months, but only 5 of 17 women who had biopsies performed had sufficient tissue for analysis. Of those with sufficient tissue, glands and stroma were sparse. The authors concluded that both doses of progesterone contained within the ring were sufficient to prevent endometrial proliferation. Participants also had fewer

days of bleeding compared to their pretreatment status. For months 2-4, 51% of participants experienced no bleeding. In addition, vasomotor symptoms, vaginal conditions including dryness, dyspareunia, discharge, and mood were improved relative to pretreatment.[52]

No consensus has been reached regarding the need for monitoring for changes in the endometrium when unopposed low-dose intravaginal estrogen is used. MacLennnan and Sturdee argued that monitoring is not required.[53] There are two elements to their argument. The first is that endometrial screening is costly and has low specificity; the second is that the risk of endometrial cancer after vaginal estrogen use is undefined. Also, estrogen-induced endometrial cancers do not appear to be associated with increased mortality thus limiting the benefits of expensive screening. There is no current consistent opinion or objective data that demonstrates the requirement for the use of progesterone in women given vaginal estrogen of any type. Endometrial proliferation requires estradiol levels higher than normal postmenopausal levels which do not consistently occur with intravaginal estrogen application. In addition, endometrial cancers often present with vaginal bleeding which makes detection easier.[53] The Cochrane Database does not show evidence of endometrial proliferation or cancers with unopposed low dose vaginal estrogen but there have been no long term studies. It does suggest that progesterone should be added if there is systemic absorption as suggested by administration of greater than 0.5 mg/day.[54]

Conclusion

For post-menopausal women who experience vaginal and lower urinary tract symptoms and do not wish to take oral estrogen, the use of intravaginal estrogen can offer significant benefit with low risk. Depending on the patient's specific needs, individualization of various treatment types and amounts is possible. It is important to counsel our post-menopausal patients about the benefits and risks of this treatment option, especially as more women are proactively seeking care that improves vaginal health and subsequent quality of life. Decisions regarding the form of intravaginal estrogen, as well as the need for intermittent progestin treatment should be individualized.

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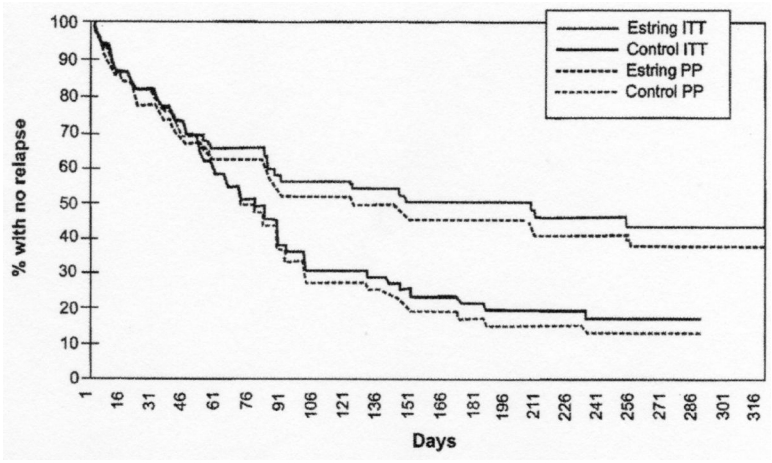

Figure 1.

Time to first recurrence curves for control and Estring-treated subjects by intent-to-treat *(ITT)* and per-protocol *(PP)* groupings. Kaplan-Meier analysis shows that cumulative proportion of subjects remaining free of urinary tract infection was significantly higher in vaginal ring group than in control group ($P = .008$ by log-rank test).

Reference: Erikson B. A randomized, open, parallel-group study on the preventive effect of an estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausat women. Am J obstet Gynecol 1999; 180: 1072-1079.

Erikson. Kaplan-Meier curve showing percent free from urinary tract infections with Estring as compared to placebo.

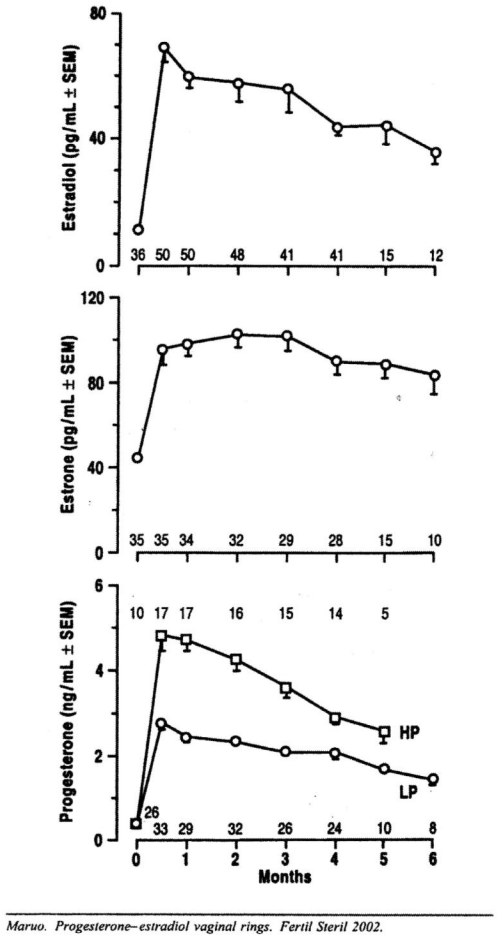

Figure 2.

Mean Serum Levels of Estradiol, Estrone and Progesterone before and during ring use. The number of subjects contributing samples is indicated for each time point. Values from users of the 2 ring types are combined for estradiol and estrone.

Reference: Maruo T, Mishell DR, Ben-Chetrit A, et al. Vaginal rings delivering progesterone and estradiol may be a new method of hormone replacement therapy. Fertil Steril 2002; 78: 1010-1016.