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Systemic Effects of Vaginally Administered Estrogen Therapy: A Review

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Abstract

Hormone Therapy (HT) was considered the standard of care prior to the publication of the Women's Health Initiative (WHI). After the study was published, the use of systemic HT dramatically decreased resulting in an increased incidence of menopausal symptoms such as hot flashes, vaginal dryness and dyspareunia experienced by women. Use of vaginal estrogen offers women a unique alternative for relief of these symptoms. This article reviews the systemic effects of vaginally administered estrogen. Effects on serum hormone levels, vasomotor symptoms, lipid profiles and use in women with breast cancer are reviewed. An accompanying review examines the local effects of vaginally administered estrogen.

Keywords

Hormone therapy; vaginal hormones; estradiol; estrone

Introduction

Until approximately 1998, "hormone replacement therapy" (HRT), or "hormone therapy" (HT) was the standard of care, buoyed by multiple observational studies that demonstrated benefit.[1-6] The use of HT was liberally recommended to women undergoing either natural or surgical menopausal with the promise of benefits for skin, bone, serum lipids, and cardiac health as well as classic menopausal symptoms. Both the Nurses Health Study[7] and the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial[8] indicated that estrogen therapy had multiple benefits ranging from cardioprotective effects to improvements in bone density.[7,8] However, these results were followed by trials that failed to find a cardioprotective benefit,[9,10] including the Women's Health Initiative (WHI),[11] which demonstrated potential harm utilizing a global index.

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In the Heart and Estrogen/Progestin Replacement Study (HERS), women with known coronary atherosclerosis were randomized to active therapy versus placebo with findings of no protective effect of hormone therapy on rates of morbidity or mortality associated with myocardial infarction (MI).[9] While the study showed no significant differences in the number of MIs or coronary heart disease (CHD) deaths in the control and study groups, there were more CHD events in the hormone group and women in the hormone group experienced more venous thromboembolic events (VTE). Similarly, the Estrogen Replacement and Atherosclerosis (ERA) study examined angiographic data in postmenopausal women with established atherosclerosis who were placed on combination hormone therapy, and found no benefit on progression of atherosclerosis.[10]

The WHI study caused a dramatic change in the recommendations for hormone therapy.[11] Results were highly publicized, especially the early discontinuation of the study secondary to increased incidence of breast cancer and cardiovascular events. The absolute risk associated with estrogen plus progestin therapy use in one year per 10,000 women was 7 more coronary heart disease events, 8 more strokes, 8 more invasive breast cancers, 18 more venous thromboembolic events, and 8 more pulmonary embolisms. On the other hand, there were 6 fewer colorectal cancers, 5 fewer hip fractures, and 44 fewer total fractures noted. However, only in the case of venous thromboembolic events were the differences statistically significant for both the nominal and adjusted confidence intervals.[12-15] Nominal confidence intervals describe the variability in the estimates that would arise from a single trial examining data for a single outcome. In contrast, adjusted confidence intervals use group sequential methods to correct for multiple analyses over time.[11] Thus the adjusted confidence intervals are more closely related to the monitoring procedures and as such, represent a conservative assessment of the evidence.[11] One criticism of the WHI is the study population, which included a group of women who were older with a mean age of 63 years at the start of hormone therapy compared to the age of onset of menopause (51 years) and likely start of HT in clinical practice. Thus the results may have not been generalizable to the younger, post-menopausal woman.[15] Also, many women in all groups had risk factors for chronic disease including tobacco use and obesity.[15]

Data from the WHI released in 2002 and subsequent papers resulted in a subsequent decrease in hormone therapy use by postmenopausal women and increase in side effects that have been a source of frustration for patients and physicians alike.[11, 16-20] While many women abandoned hormone replacement therapy following the negative press from the WHI, they were not left with an effective alternative to alleviate their menopausal symptoms. While the data of the WHI continues to be examined in additional studies of population subsets of subjects that took oral estrogen and progesterone, vaginally administered estrogen offers a unique alternative to oral therapy for some menopausal symptoms. The currently available options for vaginally administered hormones include: estradiol or conjugated equine estrogen vaginal cream, vaginal rings with estradiol or a combination of estradiol and progesterone, and estradiol vaginal tablets. The purpose of this review is to describe the **systemic** effects of vaginally administered estrogen.

Menopausal Symptoms

The impact of symptoms of menopause ranges from minimal to debilitating. Vasomotor symptoms such as hot flashes and night sweats significantly impact quality of life. While vasomotor symptoms often improve over time, urogenital symptoms do not show improvement and generally worsen with aging.[15] Atrophic vaginitis is a very common condition for postmenopausal women, which results in the sensation of vaginal dryness and dyspareunia, in up to 45% of patients.[21] In addition, women experience increased rates of urinary tract infections as well as incontinence after menopause.[22] With decreasing estrogen levels, women also experience decreased bone mass associated with an increased rate of fractures and cardiovascular disease rates that approach male levels at the same age. With the conflicting results from the use of oral hormone therapy, the use of vaginally available hormones may play an important role in the spectrum of therapeutic options for menopausal women.[22]

The Vagina as Drug Delivery System

A detailed description of the vagina as a drug delivery system germane to this review is presented in the companion review “Local Effects of Vaginally Administered Estrogen Therapy: A Review.”

Effects of Vaginal Estrogen on Serum Hormones

One way to predict the systemic effects of vaginally-administered estrogen is to examine changes in serum hormone levels. In postmenopausal women not on hormone therapy, reported estradiol levels average 14.1±0.9pg/ml and estrone levels average 27.5±1.2pg/ml.[23] The mean level of luteinizing hormone (LH) and follicle stimulating hormone (FSH) is 475 ng/ml and 2007 ng/ml, respectively.[24] Rigg and colleagues measured the levels of estradiol, estrone, LH, and FSH after application of 2 g of vaginal cream containing either 0.2 mg estradiol (E_2), 2.0 mg estradiol (E_2), or 1.25 mg conjugated equine estrogen (CEE) in six postmenopausal women.[23] Each participant rotated treatment with each type of cream. With the low dose estradiol (0.2 mg), an increase in serum estradiol was seen in 30 minutes with a peak of 80 ± 19 pg/ml reached at 4 hours. In comparison, the high dose estradiol cream (2.0 mg) led to an increase in serum estradiol that occurred in 15 minutes with its peak occurring in 4 hours at 527 ± 45 pg/ml. CEE cream showed a much slower rise of estradiol level, with a significant increase occurring after 3 hours and a peak reached at 6 hours of 33 ± 6.6 pg/ml. The low dose estradiol cream did not increase serum estrone levels until after 3 hours and was 1.6 times the basal level of estrone at 8 hours (43 ± 5.5pg/ml). The high dose estradiol intravaginal cream resulted in an increase of serum estrone after 1 hour and the estrone levels continued to increase over the 24 hours of observation. In contrast, the CEE intravaginal cream resulted in an increase of estrone after 2 hours and had a peak at 8 hours of 73 ± 9.2 pg/ml. CEE had a greater effect on serum estrone compared to estradiol levels. Both low and high dose intravaginal estradiol cream caused a greater decrease in FSH and LH than intravaginal CEE cream.[23]

In a study of 20 postmenopausal women who were at least 1 year postmenopausal, several doses of CEE (0.3, 0.625, 1.25, and 2.5 mg) were tested intravaginally for effects on levels

of estrone, estradiol, LH, and FSH.[24] Serum estrone levels were elevated greater than premenopausal late follicular phase with the CEE 2.5 mg dose (approximately 150 pg/ml compared to late follicular phase premenopausal control levels of approximately 125 pg/ml) while serum estradiol reached a level similar to the premenopausal control range (early follicular phase levels of approximately 65 pg/ml). Both FSH and LH levels decreased slightly with increasing dosage of CEE; however, both remained higher than premenopausal levels.

Dorr in 2007 reported that vaginal administration of 0.3 mg CEE cream resulted in lower systemic levels of both estradiol and estrone than oral administration of CEE 0.3 mg.[25] Serum estradiol levels reached a maximum of 12.8 pg/ml with the 0.3 mg vaginal CEE cream compared to 19.4 pg/ml approximately 8 hours after oral administration. Estrone levels reached 42 pg/ml with the intravaginal cream and 70.2 pg/ml with the oral tablets.[25]

An FDA-approved tablet form of estradiol (Vagifem®) contains 25.8 μg estradiol. Recommended dosing is daily intravaginal use for two weeks to be followed by twice weekly administration. It is well absorbed through the vaginal epithelium and circumvents the “first pass” hepatic metabolism noted with oral administration. Serum levels of estradiol and estrone are within the menopausal range after 12 weeks of use (Estradiol C max (pg/ml) 49 ± 27 on day 84, estrone C max (pg/ml) 35 ± 12 on day 84 (source Vagifem® package insert). Vagifem® is indicated for vaginal symptoms associated with menopause. According to package insert information, Vagifem® was noted to be better in improving vaginal symptoms as measured by a severity scale including dryness, soreness and irritation compared to placebo.[26]

Intravaginal estradiol is also utilized in women undergoing embryo transfer. Tourgeman et al. studied oral versus vaginal estrogen administered to women preparing for embryo transfer.[27] The women were given leuprolide, inducing a temporary menopausal state, and then administered either oral micronized estradiol (2mg bid orally or vaginally) during days 15-21 of their cycle. Two hours after the final dose of oral estradiol, mean serum levels were 279 pg/ml compared to mean serum levels following vaginal estradiol (2344 pg/ml). After homogenization of endometrial tissue biopsy specimens, estradiol levels in endometrial tissue were also determined. Orally-administered estradiol resulted in 13 pg/mg endometrial protein while vaginal application resulted in 918 pg/mg protein. While vaginally-administered estradiol resulted in ten times higher levels of serum estradiol, the endometrium showed levels 70 times higher, suggesting that the endometrium has preferential absorption.[27]

In a study by Martin et al.[28] postmenopausal women were given 0.5 mg vaginal micronized estradiol as a one time dose. Another group was given 0.5 mg vaginally with alternate day dosing for 14 days. The levels of estradiol, estrone, and gonadotropins were analyzed at 2, 4, 6, 8,10 and 24-hours post application. With the one time dose, estradiol reached a mean peak level of 1105 ± 160 pg/ml at 4 hours. At 10 hours, the estradiol level was 24 times baseline levels. In contrast, estrone reached 11 times baseline after 8 hours (exact values not given, approximately 400 pg/ml vs 0). There was a significant decrease in both FSH and LH during the first 10 hours (FSH approximately 90 to 70 mIU/ml, and LH 40 to 25 mIU/ml).[28] These

data were compared to an earlier study in which 2 mg oral estradiol was used. Use of vaginal estradiol 0.5 mg resulted in a peak serum estradiol 10 times higher than 2 mg oral estradiol (0.5mg of vaginal estradiol resulted in mean peak levels of 1105 pg/ml at 4 hours as noted above vs 2.0 mg oral estradiol esulted in peak level of 110 pg/ml at 2 hours). Estrone levels were 25% higher with the vaginal application. Oral delivery of estradiol yielded serum levels of estrone which significantly exceeded levels of serum estradiol secondary to hepatic “first pass” metabolism. However, vaginal administration of estradiol results in higher serum levels of estradiol compared to estrone because the vaginally administered estradiol is not subject to “first pass” metabolism. [28, 29]

Vaginal Estrogen and Vasomotor Symptoms Studies of vaginally-administered estrogen, both by rings and suppositories, have demonstrated relief of menopausal symptoms. Femring® is a silicone elastomer vaginal ring with a central core of estradiol acetate. There are two doses available: 12.4 or 24.8 mg of estradiol acetate delivering 50μg and 100μg of 17ß estradiol. This form of intravaginally administered estradiol was studied in postmenopausal women by Speroff for the United States Vaginal Ring (VR) Investigational Group.[30] Both formulations were significantly better than placebo in decreasing both the number, frequency, and severity of moderate to severe vasomotor symptoms.[30] By week 12 the number of moderate and severe vasomotor symptoms in the placebo group was 42.2 versus 15.5 in the 50μg E_2 ring and 8.3 in the 100μg ring ($p<0.05$).

Foidart et al studied 109 women treated with vaginal suppositories containing 3.5μg estriol twice weekly for three weeks followed by one suppository weekly for six months or placebo and demonstrated significant reduction in vasomotor symptoms as assessed by the Kupperman index including hot flushes and other symptoms. [31] Likewise, Vartiainen studied the effects of a vaginal ring containing 53 mg of 17β estradiol vs placebo on vasomotor symptoms in 26 women. Women treated with the estradiol-containing ring demonstrated a significant reduction in symptoms.[32, 33] Serum estradiol levels similar to the follicular phase of premenopausal menstrual cycles were measured after 1 month of use and serum estradiol levels remained above post menopausal values. FSH was suppressed, however LH was not. Postmenopausal complaints were reduced during use of the ring.

Vaginal Estrogen: Lipid Profiles and Bone Density

Vaginal estrogen therapy may have a positive impact on serum lipid profiles. In a recent study, women over 60 years of age were randomized to receive Estring® (7.5 μg) or placebo. Compared to controls, the treatment group was noted to have non-significant increases in serum estrone (16%) and estradiol (13%), however Estring® resulted in a decrease in LDL by 7.6%, an increase in HDL by 25%, and a decrease in total cholesterol by 4%. These results are similar to effects of commonly used patches and oral CEE.[34] In another study, Naessen et al studied changes in serum lipids in 70 healthy women greater than 60 years old treated with a vaginal ring delivering E_2 7.5μg per 24 hours (Estring®) or placebo for 12 months. Estring treatment was associated with non-significant increases in estrone (+16%), and estradiol (+13%) within the normal postmenopausal range. The serum LDL cholesterol decreased by 7.6% (P=0.014) and LDL to HDL ratio by 7.3% (P=0.030). Total cholesterol levels were significantly reduced (4%), and triglycerides were not increased. No significant

changes were noted in the control group. The authors concluded that ultra-low doses of E_2 may improve lipid levels in older women with a pattern and magnitude similar to that previously reported for conventional estrogen doses or first generation lipid lowering agents.[34]

Estrogen plays a very important role in bone health. In a study of postmenopausal women, a serum estradiol level less than 5 pg/ml resulted in an increased relative risk of 2.5 for hip and vertebral fractures compared to postmenopausal women with estradiol levels greater than 5 pg/ml.[35] In addition, if sex hormone binding globulin (SHBG) levels were higher than 1 μg/dL, the relative risk was 2.0 for hip fracture and 2.3 for vertebral fracture compared to those with a lower SHBG level.[35] While oral estrogen replacement therapy is known to improve bone health as shown in the PEPI and WHI trials, it is unclear whether long-term use of vaginal estrogen is protective of bone mineral density. In a randomized trial of Estring® 7.5 μg/day versus placebo in women over 60 years old, after six months, individuals who received Estring® had an increase in their forearm density of 2.1% compared to individuals on placebo who had a decrease of 2.7%.[36] There was a decrease in osteocalcin and alkaline phosphatase in those taking Estring®, suggesting reduced turnover, while individuals on placebo had no change in these markers. Thus, even low dose vaginal estrogen may result in favorable effects on bone.[36]

Vaginal Estrogen and Breast Cancer

Another controversy in HT, is its use for menopausal symptoms after a diagnosis of breast cancer. Currently, women with breast cancer often suffer from menopausal symptoms because they may be diagnosed while premenopausal and oopherectomy may be performed as part of the therapeutic regimen. In addition, adjuvant treatments for breast cancer, including chemotherapy regimens can result in premature ovarian failure, and aromatase inhibitors, which have anti-estrogen mechanisms, can cause marked menopausal symptoms. Serum estradiol levels average 500 pmol/ml (136.2 pg/ml) in premenopausal women and fall to approximately 25 pmol/L (6.81pg/ml) in postmenopausal women.[37] Standard oral estrogen therapy results in an average estradiol level of 170 pmol/L.[37] The WHI showed an increase in the Relative Risk (R.R.) of developing breast cancer with combined hormone therapy, utilizing oral CEE 0.625 mg and medroxyprogesterone acetate 2.5 mg above controls.[11]

Vaginal estrogen use may be ideal for the treatment of menopausal symptoms in women following a diagnosis of breast cancer. As noted above, most forms of vaginal estrogen, with the exception of high dose vaginal cream and Femring® lead to serum estradiol levels that are within the menopausal range. The goal of vaginal estrogen in these cases would to be to relieve local symptoms without an increase in serum estrogen levels. For urogenital symptoms, the vaginal ring that provides 5-10 μg/day locally and results in no increased serum estradiol, even if an ultra-sensitive bio-assay is used, meets these requirements. If vaginal estradiol less than 25 μg twice weekly or vaginal estriol less than 0.5 mg twice weekly is administered, there is no associated increase in serum estrogen.[37] Expert opinion suggests that oral and transdermal hormone therapy are currently contraindicated for at least

some women with a diagnosis of breast cancer.[37] However, vaginal estrogen may provide relief of vaginal symptoms without an increase in serum levels.[37] (Table 1).

An exception to this situation, however, may exist in women taking aromatase inhibitors. A recent study reported that in women using aromatase inhibitors, baseline serum estradiol was less than 5 pmol/l (1.36 pg/ml). After 2 weeks use of Vagifem® vaginal estradiol tablets, serum levels reached a mean concentration of 72 pmol/l (19.6 pg/ml). This level fell to less than 35 pmol/l (9.5 pg/ml) at 4 weeks except for two women where the estradiol remained elevated. The authors concluded that Vagifem® may counteract estrogen suppression caused by aromatase inhibitors and should not be used with these agents.[38]

Conclusion

Intravaginal estrogen is an important option which physicians may utilize for the symptomatic treatment of menopausal symptoms. Intravaginally administered estrogen can have effects beyond treatment of atrophic vaginitis, including improvement of vasomotor symptoms, and possibly lipid profiles and bone density. For women with breast cancer, low dose intravaginal estrogen may be an option for treatment of urogenital symptoms. It is unclear what endometrial cancer risk elevation is associated with intravaginal estrogen, and thus some authors recommend periodic progesterone, while others cite data showing very low rates of hyperplasia to support no need for periodic progesterone or biopsy (see other review).

The role of vaginal estrogen will continue to increase in the treatment of menopausal symptoms secondary to a lower side effect profile compared to oral administration as well as patients' tolerance and high level of satisfaction with its use.[39,40] One potential limiting factor for the use of vaginal estrogen is patients' misinformation about vaginal anatomy. If patients can be reassured about ease of administration and effectiveness for symptoms, they will be more likely to continue use and obtain symptom relief resulting in improved quality of life.

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Table 1

Serum levels following vaginal estrogen administration

studies on low dose vaginal estrogens: systemic absorption and endometrial effect

study	Nr. Of pts.	Type of Study	Drug	Type of preparation	Dose	Duration	Mean E2 serum levels over 24 h (pg/ml)	Endometrial thickness (mm)
Simunic [43]	1612	Double Blind placebo-controlled	17P-E2 *vs.* Placebo	Vaginal Tablets	25 μg/day for 2 wks; then 25 μg twice/wk	12 mo	Basal: 15.7 *vs.* 14.2 (*p*=0..346) At 4 mo: 17.3 *vs.* 15.1 (*p*=0.456) At 12 mo: 15.5 *vs.* 13.8 (*p*=0.322)	Basal: 3.1 *vs.* 3.2 (*p*=0.432) - At 12 mo: 2.9 *vs.* 3.0 (*p*=0.324)[a]
Notelovitz [48]	58	Double-masked, randomized parallel group	17P-E2	Vaginal tablets	10 vs. 25 μg/day	12 wks	Basal: 7.0 *vs.* 7.6 (*p*=ns) At 1 wk: 15 *vs.* 22(*p*=ns) At 12 wks: 11 *vs.* 23 (*p*=ns)	
Santen [42]	7	Single-blind, single arm	17β-E2	Vaginal Cream	10 μg/day for 3 wks; then 10 μ % twice/wk	12 wks	Basal: 1-3 At 24 h, 3 & 12 wks: 3-5 (*p*=ns)[b]	Basal < 5mm At 12 wks < 5mm
Dugal [49]	96	Randomised parallel group, single blind	17β-E2 *vs.* Estiiol	Vaginal tablets *vs.* vagitories	25 μg/day for 2wks; then 25 μg twice/wk *vs.* 0.5 mg/day for 2wks; then 0.5 mg twice/wk	24 wks	Basal: <30 with both treatments (*p*=ns) At 2, 12 and 24 wks: <30 with both treatments (*p*=ns)	Increased during the first 2 wks with both treatments (1.1 mm *vs.* 0.5 mm) but returned to baseline by the end of study (*p*=ns)
Nilsson [40]	6	Single arm	17β-E2	Vaginal tablets	25 μg/day for 2wks; then 25 μg% twice/wk	12 wks	Basal: 7.4 At 12 wks: 13.6 (*p*=ns)	
Naessen [50]	60	Randomised, non-placebo controlled	17β-E2 *vs.* no treatment	Vaginal ring	7.5 μg/day	12 mo	Basal: 13.5 *vs.* 15.3 (*p*=ns) At 12 mo: 15 *vs.* 15.38 (*p*=0.15)	Basal: 1.08 *vs.* 1.36 (*p*=ns) At 12 mo: 0.94 *vs.* 1.18 (*p*=0.54)

Abbreviations. E2, estradial; mo, months; wk, week; Nr, number; Pts, patients; and ns, not significant.

Reference: Ponzone R, Biglia N, Jacomuzzi ME, et al. Vaginal Oestrogen Therapy After Breast Cancer: Is It Safe? Eur J Cancer 2005; 41:2673-2681

[a] Vaginal bleeding in 5 (0.6%) *vs.* 0 patients (p=ns).

[b] Mean 2pg/ml increase only during the first 4 h after administration.