Estriol: Safety and Efficacy

by Kathleen A. Head, N.D.

Abstract

While conventional hormone replacement therapy provides certain benefits, it is not without significant risks. Estriol has been found to provide some of the protection without the risks associated with stronger estrogens. Depending upon the situation, estriol may exert either agonistic or antagonistic effects on estrogen. Estriol appears to be effective at controlling symptoms of menopause, including hot flashes, insomnia, vaginal dryness, and frequent urinary tract infections. Results of research on its bone-density-maintaining effects have been contradictory, with the most promising results coming from Japanese studies. Estriol's effect on cardiac risk factors has also been somewhat equivocal; however, unlike conventional estrogen prescriptions, it does not seem to contribute to hypertension. Although estriol appears to be much safer than estrone or estradiol, its continuous use in high doses may have a stimulatory effect on both breast and endometrial tissue.
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Introduction

A significant problem facing peri- and postmenopausal women, as well as their healthcare practitioners, is determining what approach to take regarding hormone replacement. There are many options, ranging from no intervention at all to conventional hormone replacement therapy (HRT). Approaches which lie somewhere in between involve the use of herbal and nutritional approaches or the use of "friendlier" more gentle hormone replacement regimes than those typically prescribed. One of the hormones which has been virtually ignored by conventional medicine but which shows some promise of effectiveness without as many side-effects is estriol. Its use is increasing in popularity, prescribed either alone or in the form of triple estrogen (80% estriol, 10% estrone, 10% estradiol). The purpose of this article is to examine the research on this hormone to determine its effectiveness in the treatment of peri- and postmenopausal conditions — hot flashes, osteoporosis, cardiovascular risk; and to determine its safety, particularly in regard to cancer risk.

Biosynthesis, Metabolism, and Excretion of Estrogens

Estrogens are steroids whose immediate precursors are either androstenedione or testosterone. (See Figure 1.) These precursors are synthesized primarily in the ovaries, adrenals, and testes. Estradiol, produced by androgenic precursors, is the principle estrogen secreted by the ovaries premenopausally. Secreted estradiol is oxidized reversibly to estrone, and both of

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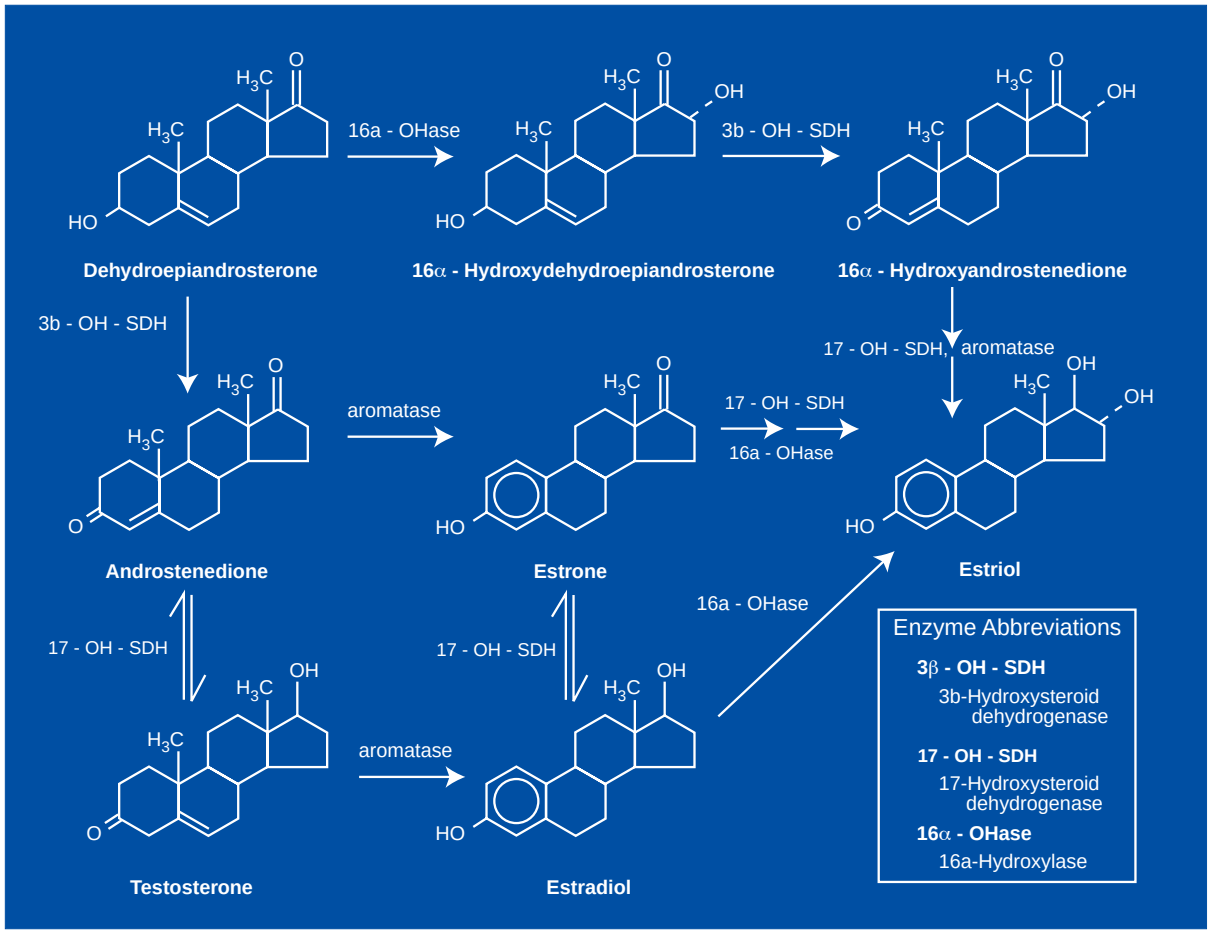
Figure 1. Biosynthesis of estrogens



these estrogens can be converted to estriol. These conversions take place primarily in the liver. While there appears to be some level of enterohepatic recirculation of estriol, it appears to be somewhat less than that for other estrogens.[1]

Longcope studied the levels of circulating estriol in postmenopausal women, and also in premenopausal women during both the follicular and luteal phases. It appears to be present at low but fairly steady concentrations throughout the day and throughout the menstrual cycle, with a slightly higher level noted during the luteal phase. The levels that do exist are far lower than those for estrone and estradiol. Most estradiol, however, is bound to sex-hormone binding globulin (SHBG), so only a portion of the circulating estradiol is available for entry into cells. On the other hand, estriol has a much lower affinity for binding to SHBG; therefore, a greater percent is available for biological activity.[1]

In his study on estriol production, Longcope found something unexpected. While it is commonly believed most estriol results from conversion of estradiol and estrone, in his study there was evidence of no more than 0.4 percent peripheral conversion of either estrone or estradiol. The researchers concluded either there is a small secretion of estriol directly from the adrenals or ovaries of reproductive-age women, or that other precursors exist.[1] Other researchers have found similar ratios of radio-labeled estrone and urinary estriol, indicating most of the estriol had come from estrone.[2] Longcope noted others have reported direct conversion of androstenedione to estriol without passing through the blood pool of estrone.[1]

In men and in postmenopausal women the principle site of estrogen secretion is adipose tissue, where estrone is formed from dehydroepiandrosterone (DHEA), which is secreted by the adrenal cortex. In addition to circulating estrogens secreted by the ovaries, estrogens may be produced locally and may play a causal role in certain disease states such as breast cancer. All three estrogens are excreted in the urine.[1]

Pharmacokinetics of Estriol

Pharmacokinetic studies of estriol and its effect on target tissues have been contradictory, with dosage and routes of administration appearing to be key factors. The effects of oral and vaginal administration of unconjugated estriol were studied. One mg intravaginal estriol resulted in serum levels equivalent to 10 mg of the orally administered hormone. Vaginal application circumvents the first pass through the liver, where a large portion of estriol is immediately conjugated, an action believed to contribute to the short duration of action of the orally-administered hormone. On the other hand, entero-hepatic recirculation, which is enhanced by periodic fat-rich meals, results in prolonged elevation of plasma estriol levels, thus enhancing the potency of estriol.[3] These same researchers found the administration of activated charcoal resulted in binding of estriol in the colon and subsequent excretion via the feces, stopping the recirculation process and leading to a rapid decline in plasma estriol levels.

Estriol levels spike for about 3-4 hours after a daytime oral dose; a meal after four hours results in a second spike. The dietary effects on vaginal administration, due to the diminished importance of entero-hepatic circulation, are negligible. Therefore, some researchers report vaginal administration offers a more standardized regime; whereas, oral administration is affected by many variables.[3]

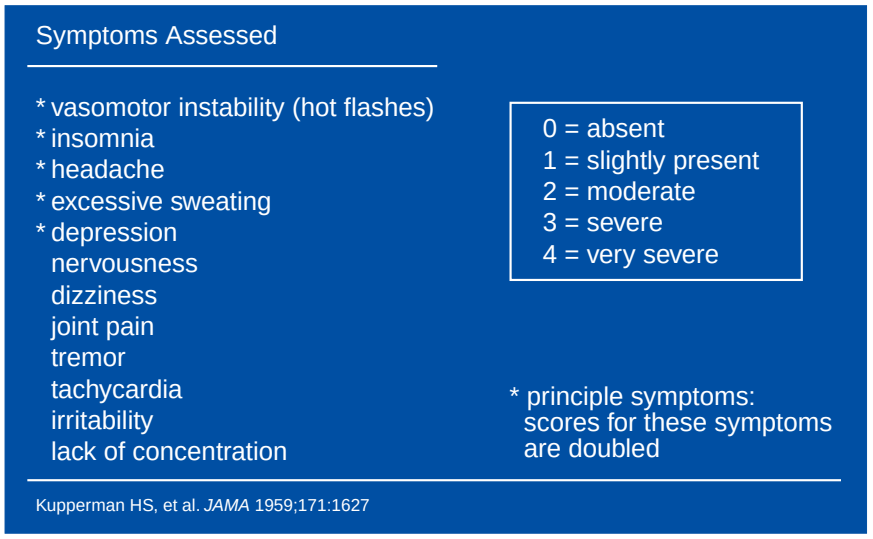
Estriol appears to have both estrogenically antagonistic and agonistic effects. When given alone, it generally exerts an estrogenic effect, the strength of which depends on the dosage. When given in conjunction with estradiol, it appears to exert antagonistic effects.[4] Researchers have also found estriol to be an estrogen antagonist when given as a short-burst bolus.[5] Others have found estriol to be a short-acting agonist when administered in a single dose. In addition, *in vitro* studies have found estriol competes with estradiol binding, offering a mechanism for its antagonistic effects.[6]

Estriol for the Management of Menopausal Symptoms

Because of concern with conventional hormone replacement protocols regarding the increased risk of certain cancers—particularly breast and endometrial—as well as other conditions such as liver and gall bladder disease, thromboemboli, and hypertension, clinicians and patients are continually searching for a less toxic approach to menopausal hormone replacement. A review of the literature is provided below to help determine the effectiveness and dosage requirements of estriol.

Tzingounis et al studied the use of estriol on 52 postmenopausal women to determine its effect at varying dosages on vasomotor instability (as determined by hot flashes), vaginal cytology, vaginal mucus, and endometrial proliferation. Serum levels of FSH, LH, estrone, and estradiol were taken before, during and after this six-month trial. Mammograms were also administered when indicated. Subjects were divided into four dosage groups: 20 received 2 mg/day, 16 received 4 mg/day, and two groups of eight received either 6 or 8 mg/day. All patients selected for this study had severe menopausal symptoms. In all patients menopausal symptoms were decreased, the degree of

Figure 2. Kupperman index for subjective assessment of menopausal symptoms



improvement reflecting the dosage administered. Those taking 8 mg/day demonstrated the most dramatic diminution of symptoms as measured by the Kupperman index. (See Figure 2.) In all subjects who underwent endometrial biopsy, including some who experienced initial spotting, there were no signs of endometrial hyperplasia. All PAP smears remained class I, and there were no abnormalities noted on CBC, SMA-18, or urinalysis. Mammograms obtained on six patients who had mammary hyperplasia at the outset of treatment remained unchanged with therapy. Weight and blood pressure of all subjects remained stable.[7]

Yang et al reported on 20 women who had undergone either natural or surgical menopause, and were treated with 2 mg/day estriol succinate for two years. They reported estriol to be very effective at relieving subjective symptoms, especially hot flashes and insomnia, in 86 percent of patients within three months. Atrophic vaginal changes seen during menopause also were improved satisfactorily. No participants complained of subjective side-effects, and only one exhibited minor uterine bleeding the first month.[8]

Perovic et al studied the effect of 1 mg estriol for two years on 150 menopausal women. The Kupperman index was used to measure subjective complaints. The average score prior to therapy was 34, but it decreased considerably during the first, second, and third months of the trial, to 20, 10, and 6, respectively. Urinary estriol excretion patterns returned to nearly normal in most cases. No malignant changes were observed in genital organs, as assessed by vaginal smear and gynecological exam every six months. There were no complaints of side-effects, with the exception of bleeding in eight patients after several months of treatment, which stopped after several days.[9]

Does Estriol Decrease Cardiac Risk?

Estrogen, either with progestin or unopposed, has been found to lower cardiac risk factors in postmenopausal women. In The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, both regimes, but especially unopposed estrogen, significantly improved lipid profiles and lowered fibrinogen levels.[10] In the Nurses' Health Study, postmenopausal hormone therapy appeared to reduce the risk of mortality the most dramatically in those subjects with the highest coronary risk.[11] Japanese researchers found that estriol at 2 mg/day was effective in decreasing total cholesterol and triglycerides, and increasing HDL levels in elderly women (age 70-84), but not in middle-aged postmenopausal women (age 50-65).[12]

A synthetic estriol derivative called nylestriol was tested in two Chinese studies[13,14] to determine its effect on cardiac risk factors. In one- and three-year studies, the administration of 2 mg every two weeks resulted in elevation of HDL levels, lowering of LDL, and

no change in total cholesterol or triglyceride levels. The dosing schedule of the synthetic derivative was due to it being a longer-acting, stronger estrogen, as evidenced by the fact that one-third of subjects had spotting and another one-third had withdrawal bleeding after administration of medroxyprogesterone acetate. This is in opposition to estriol's activity as a safer, weaker, short-acting estrogen.

Conventional estrogen replacement therapy has sometimes been associated with an increased incidence of hypertension, due to the effect on renin activity and aldosterone. A Finnish study measured the effect of 2 mg/day estriol succinate on plasma renin activity and urinary aldosterone in postmenopausal women on both short-term therapy (after three months), and long-term therapy (after 5-8 years). No effects were found on the renin-aldosterone system to suggest estriol might contribute to hypertension.[15]

Toy et al studied the effect of estriol succinate supplementation on hemostatic mechanisms in postmenopausal women in an attempt to determine whether estriol is safer than other more conventional estrogen interventions. They concluded estriol succinate may have less thrombotic potential than synthetic estrogens.[16] More studies on natural estriol and its effect on cardiovascular risk factors in postmenopause are needed.

Estriol's Effect on Osteoporosis Prevention

A question which faces many practitioners prescribing estriol for their patients is whether it will effectively prevent bone loss. A number of researchers have put it to the test. Yang et al measured bone mineral density (BMD) of the lumbar spine using quantitative computed tomography after one and two years of treatment with 2 mg/day of estriol succinate. The control group received estradiol. While the estradiol effectively prevented loss of bone mass, the estriol did not.[8] A group of Italian researchers compared two groups, one receiving calcium alone, and one receiving calcium plus estriol administered intravaginally at a dosage of 0.5 mg every other day. Both groups demonstrated a decline in BMD, although the decline was blunted in the estriol group. The addition of salmon calcitonin as a nasal spray resulted in markedly increased bone mineral density.[17]

Several Japanese studies yielded somewhat different results. Seventy-five postmenopausal women with bone densities more than 10 percent below peak were given estriol at 2 mg/day along with 800 mg daily calcium lactate. This resulted in an average increase in BMD of 1.79 percent after 50 weeks as measured by dual energy x-ray absorptiometry (DXA).[18] Another Japanese study found an increase in BMD following estriol treatment. Seventeen women 10 years postmenopause were given 2 mg/day estriol and 2 gm/day calcium lactate for one year. They were compared to a group of nine women who received 2 grams calcium lactate only. BMD was significantly reduced at the end of the study period in the calcium-only group, while the estriol-plus-calcium group demonstrated a 1.66 percent increase in BMD, using the DXA method of evaluation.[19] Biochemical markers of bone metabolism include alkaline phosphatase, which is a measure of bone formation, and pyridinoline and deoxypyridinoline, which are both measures of bone resorption. Estriol administration resulted in a decrease in all of these biochemical markers, indicating estriol appeared to work by preventing acceleration of the postmenopausal bone loss normally seen.[19]

A third Japanese study tested the effect of estriol on BMD in postmenopausal as well as "senile" osteoporosis. They administered 1 gm/day calcium lactate, alone or in conjunction with 2 mg/day estriol to 20 postmenopausal women (age 50-65) and 29

elderly women (age 70-84) for 10 months. DXA evaluation of BMD of the lumbar vertebrae yielded the following results: Of 41 subjects who completed 10 months of treatment, eight postmenopausal and 12 elderly subjects in the estriol group exhibited significant increases in BMD (5.59 ± 4.79% of the respective basal values). Ten postmenopausal and 11 elderly women in the control group had decreased BMD (-4.02 ± 7.00% and -3.26 ± 4.60% of the respective basal values).[12]

A study on 28 postmenopausal women in Scotland taking a high dose of 12 mg/day estriol for two years did not find it protective from bone loss as measured by the DXA method. Twenty-four of the 28 patients demonstrated an average rate of bone loss of 1.9 percent per year. Fourteen patients receiving 4-6 mg/day demonstrated an average bone loss of 2.7 percent per year, while a previous ongoing placebo group demonstrated an average rate of bone loss of 3.6 percent per year.[20] Thus, the protective effect appears to be dose dependent; however, despite the fact that estriol slowed the bone loss, these researchers found dosages as high as 12 mg/day did not offer sufficient protection.

The long-acting estriol derivative, nylestriol, was found to arrest bone loss in both one- and three-year studies. The trade-off for a higher potency, synthetic derivative, however, was endometrial stimulation necessitating progestin therapy to correct it.[13,14]

It is interesting to note that all the positive studies on estriol for the prevention of osteoporosis were conducted in Japan. It is this author's speculation that the Japanese diet, high in phytoestrogens from soy products,[21] potentiates the effect of estriol in this population. This points to the importance of diet as well as hormone replacement in the prevention and treatment of osteoporosis. Both progesterone and synthetic progestins have been found not only to slow bone loss but to increase bone density, as progesterone is a bone-trophic hormone.[20,22] Thus, addition of progesterone should be considered when designing a program for osteoporosis prevention.

Estriol's Effect on Atrophic Vaginitis and Postmenopausal Urinary Tract Problems

Other problems associated with menopause include atrophic vaginitis, with its subsequent vaginal dryness, dyspareunia, and increased frequency of vaginal infections; and atrophic changes in the urinary tract associated with increased tendency for urinary tract infections (UTIs), incontinence, frequency, and urgency.

Hustin et al studied vaginal cytology via the maturation index in 263 menopausal women, divided into groups receiving varying doses of either synthetic estrogens or estriol. In doses of 33-66 mcg/kg/week (or roughly 2-4 mg per week) estriol was able to restore normal vaginal cytology. This dose was 3-5 times lower than that necessary to cause endometrial stimulation. Unlike estriol, the therapeutic doses of the various estradiols given were in the same range as those which caused endometrial hyperplasia.[23]

A German randomized double-blind trial of 15 postmenopausal women found local treatment with vaginal tablets containing 0.03 mg estriol in conjunction with *Lactobacillus acidophilus* provided complete restoration of the normal vaginal milieu.[24] Van der Linden et al reported on the remarkable effect of estriol in restoring atrophic vaginal and urethral epithelium in 62 postmenopausal women. They were given descending doses of estriol (8 mg/day the first week, 4 mg/day the second and third weeks, and 2 mg/day the fourth week) or placebo. Vaginal epithelium was restored in the estriol group as measured by both the maturation index and karypicnotic index.[25] Heimer used somewhat lower doses (0.5 mg/

day) to induce a restoration of both vaginal and urethral epithelium in 41 women with urogenital disorders associated with atrophic changes. No changes in urinary bacterial flora were detected during the short study of only two weeks duration.[3]

Clinically, estriol appears very effective for the treatment of menopausally-related urinary incontinence, urgency, and persistent UTIs. Schar et al reported on the use of 3.5 mg estriol intravaginally for three months in the treatment of 135 postmenopausal women with urinary incontinence. Symptoms were assessed according to a Gaudenz questionnaire. All eight symptoms improved significantly, with 63 percent of patients showing improvement in incontinence, and 50 percent showing improvement in urinary stress incontinence. Dysuria, reported in 14 subjects at the onset of treatment, was completely resolved in all cases. Both daytime and nighttime urinary frequency diminished significantly.[26] Another study which examined estriol for the treatment of nocturia and urge incontinence found both estriol at 3 mg/day and placebo equally effective at reducing urgency and nocturia.[27]

Another double-blind, placebo-controlled study examined the effect of intravaginal estriol or placebo on the incidence of urinary tract infections and vaginal dysbiosis in a population of postmenopausal women with recurrent UTIs. After eight months the incidence of infection in the estriol group was significantly reduced compared to the placebo group, with 0.5 versus 5.9 episodes per patient year. It was also noted that Lactobacillus was absent in all vaginal cultures before treatment but reappeared after one month in 22 of 36 of the estriol treated group and in none of the placebo group. Furthermore, average vaginal pH declined from 5.5 to 3.8 in the estriol group, with no significant change in the placebo group. Vaginal colonization with Enterobacteraceae fell from 67 to 31 percent in the estriol group and only from 67 to 63 percent in the placebo group. The conclusion of these authors was estriol successfully prevented recurrent UTIs by modifying vaginal flora.[28]

Estriol's Effect on the Skin

Estrogen is an important hormone for maintaining skin elasticity. The effect of local estriol treatment on abdominal skin was examined in 14 postmenopausal women for three weeks. Six control subjects received an ointment without estriol. The application of estriol for this short period of time resulted in thickened, better-oriented, and slightly increased numbers of elastic fibers in half the patients using the estriol cream, compared to no change in the placebo group.[29]

Topical use of estriol was effective for the treatment of premenstrual acne as measured by number of skin lesions and thin-layer chromatographic sebum-determination from treated and untreated areas.[30] In another study, topical estriol administered via iontophoresis was compared to tretinoin (trans-retinoic acid) iontophoresis for treatment of acne scars. Eighteen women were treated with estriol iontophoresis twice weekly for three months. The results were compared with a group of 28 patients (19 women and nine men) who received tretinoin iontophoresis according to the same schedule. Improvement of acne scars was observed in 93 percent of the tretinoin group and 100 percent of the estriol group. Typical side-effects of dry skin and retinoid dermatitis were observed in four in the tretinoin group but in none in the estriol group.[31]

Safety of Estriol

Concerns about the safety of estrogen replacement therapy, particularly in regard to its contribution to the risk of hormone-related cancers such as uterine and breast, have led researchers to explore the effect of estriol on uterine endometrial and breast tissue.

Effects on Endometrium: It is well established that unopposed estrogen may contribute significantly to the development of uterine cancer.[32,33] It is commonly believed estriol does not contribute to endometrial proliferation in the same way as estradiol and estrone. However, Wren studied a small group (23 women) who were given various doses of estriol ranging from 1-8 mg/day to control hot flashes and other symptoms of menopause. They were also given a synthetic progestin for 10 days of the month. Because 2 of the 11 women with intact uteri had regular monthly withdrawal bleeding over the six months of the trial, the authors surmised the estriol was contributing to some endometrial stimulation.[34] However, withdrawal bleeding or spotting can not be considered proof of endometrial proliferation, as any endometrium is subject to bleeding.

Histological examination of uteri from hysterectomized women confirmed that a three-week vaginal application of either estriol (8 recieved 0.5 mg estriol) or estradiol (9 received 0.05 mg estradiol) contributed to stimulation of the endometrium. The endometria of all 12 women in the control group remained atrophic.[35] An animal study by Clark et al found all three types of estrogen, when administered continuously, resulted in significant increase in uterine weight. They found estriol, however, to be an estrogen antagonist when given as a short-burst bolus.[5]

Montoneri et al studied 50 women (age 55-81) with uterine prolapse awaiting hysterectomy. Forty-eight of the 50 women had endometrial atrophy as determined by histological exam. Excluding the two with hyperplasia, 48 were treated with oral estriol, 1 mg twice daily for 10 to 25 days prior to hysterectomy. Histological exam of the uteri post-hysterectomy showed hyperplastic changes in 70.8 percent of the women.[36] While 22 of the 48 women also received conjugated estrogen vaginal suppositories along with oral estriol, the difference between the group receiving estriol only versus estriol and conjugated estrogens was statistically insignificant.

An interesting study compared the effect of varying dosage schedules on endometrial proliferation. Postmenopausal women, four in each group, were given oral dosages of estriol succinate (either one dose of 8 mg/day, 4 mg twice daily, or 2 mg am, 2 mg noon and 4 mg evening) for four weeks. A fourth group received 4 mg twice daily for only 14 days. Endometrial curettage samples were examined before and after hormone therapy. In this study, at least four weeks was necessary to effect a change in the endometrium. Only a slight effect was noted in the endometrium of those receiving one 8 mg dose daily; but clear proliferative changes were noted when the dose was divided.[37] It may be that estriol's effect on the endometrium has less to do with the dose and more to do with the frequency of administration, with more frequent dosages being more likely to contribute to endometrial hyperplasia.

Notwithstanding the above, a meta-analysis of 12 studies, examining 214 women who had been continually using estriol vaginal cream, disclosed quite different results. A total of 337 post-baseline biopsies were reported at varying stages of treatment, ranging from six months to two years after beginning estriol use. All 337 endometrial biopsies were classified as atrophic. These authors concluded daily use of intravaginal estriol is safe and without risk of endometrial proliferation or hyperplasia.[38] As previously mentioned, Tzingounis et al found no endometrial changes in 52 women given 2,4,6 or 8 mg/day estriol for six months.[7] It is this author's experience that continuous use of either triple estrogen (2 mg estriol, 0.25 mg estrone, and 0.25 mg estradiol) or estriol (2.5 mg), both with 50 mg progesterone, and given in divided doses of three to four times daily, did not result in endometrial hyperplasia in about a half-dozen

Table 1. Epidemiological examination of estrogen quotients and breast cancer risk

Location	(Population) Ratio estriol / estrone + estradiol, follicular; luteal			
	High Risk	Intermediate	Low Risk	Significance
Zambia pre-men.	(European Cauc.) 0.64 - 0.83	(African) 0.76 - 1.02	(Indian) 1.16 - 1.48	<0.01 (luteal)
Honolulu pre-men. 15-24 years	(Caucasian) 0.57 - 0.71	(Chinese) 0.84 - 1.21	(Japanese) 0.76 - 0.98	<0.001
North America Honolulu vs., Japan, Hong Kong Taiwan pre-men. 15-24 years	(Caucasian) 0.59 - 0.74	(Asian decent) in Honolulu 0.80 - ... (Caucasians) in Honolulu 0.61 - ...	(Asian) 1.41 - 1.43	<0.01
United Kingdom vs. Japan pre-men 17-30 years	(Caucasian) 0.9 - 0.97 +/- 0.6		(Japanese) 0.9 - 1.2 +/- 0.6	n.s.
United Kingdom vs. Hawaiian Japanese vs. Japan under 32 years	(Caucasian) 0.46	(Japanese in Hawaii) 0.46	(Japanese) 0.51	n.s
Israel post-men. 50-59 years	(European caucasian) 1.19 *	(African, Asiatic origin) 2.16 - 2.17 *	(Yemeni) 2.54 *	<0.001

* Estriol / Estrone

Adapted from Lemon[44]

patients for whom endometrial biopsies were performed due to uterine bleeding. Due to conflicting reports on the effect of estriol on the endometrium, it is probably wise to prescribe a natural progesterone in conjunction with the estriol for a period of at least 10-14 days per month in order to shed any uterine tissue which may have built up as a result of the estriol administration.

Breast cancer risk: For many years it has been believed exogenous estrogen can contribute to the etiology of breast cancer. Several relatively recent studies have proven that to be the case. A large 1991 meta-analysis found an increased risk for breast cancer started to appear after five years of taking estrogen replacement, and after 15 years of taking estrogen, the average risk increased 30 percent over those not taking estrogen. In women with a family history of breast cancer, use of estrogen for any length of time resulted in a significantly increased risk.[39] In 1997, the results of the large-scale Nurses' Health Study disclosed that, while hormone replacement resulted in decreased risk of death from all causes, the benefit decreased with long-term use because of increased mortality from breast cancer in long-term users (10 or more years).[11] The use of estrogens with and without progestin was studied relative to breast cancer risk. A substantial increase in risk was noted in women who took hormone replacement; and addition of progestin did not reduce the risk.[40] In fact, in a Swedish study the risk was actually increased with the addition of synthetic progestins.[41]

The search for safer hormone replacement has led researchers to study the safety of estriol in regard to breast cancer risk. Animal studies have demonstrated a protective effect of estriol when given to rats prior to exposure to the breast-tumor-inducing carcinogen, dimethylbenzanthracine.[42] Researchers have also noted decreased urinary excretion of estriol in breast cancer patients when compared to subjects without breast cancer.[43] An analysis of six epidemiological studies of estrogen quotients (estriol/estrone+estradiol) found higher estrogen quotients (more estriol in relation to estrone and estradiol) in populations with lower risks of breast cancer.[44] (See Table 1.)

Pratt et al however, has not found a correlation, either between the levels of urinary metabolites of the various estrogens and breast cancer risk or, for that matter, a correlation between the ratio of these hormones in plasma and in urine. Their sample size, however, was very small – just seven women who had had breast cancer and five who had not.[45]

One of the leading researchers on estriol, Henry Lemon, MD, of the University of Nebraska, postulated that estriol is probably a safer form of estrogen replacement in regard to breast cancer for the following reasons: 1) *In vitro*, when given in conjunction with estradiol, it accelerates the removal of estradiol bound to protein receptors; 2) investigators have been able to initiate very little carcinogenesis in animal studies unless large doses (200-500 mcg/kg/day) were used on a continuous basis; 3) in animal studies it has been found to prevent carcinogen-induced mammary tumors; and 4) unlike estrone and estradiol, estriol metabolism does not result in the formation of large numbers of potentially carcinogenic substances.[44]

Lemon reported clinical results with the use of estriol in breast cancer patients. He prescribed estriol (5-15 mg daily) to 24 patients with existing metastases. He found an increased growth of metastases in six patients. There was no evidence of change in the uninvolved normal breast over a period of 15 patient years. Two of the 24 patients developed adenomatous endometrial hyperplasia after 8-40 months of treatment. He postulated that lower doses and an intermittent schedule of dosing, such as every other day, would provide more potential for protection from mammary carcinogenesis and endometrial hyperplasia.[44]

Follingstad reported further on unpublished data from Lemon et al. After informed consent, postmenopausal women with breast cancer were supplemented with 2.5-5 mg (a few received 15 mg) estriol daily. Thirty-seven percent demonstrated remission or arrest of metastatic lesions. It is unclear whether this was the same group of women cited above, and if so, why Lemon did not report this arrest of metastases.[46]

In vitro studies have demonstrated that estriol, as well as estrone and estradiol, has a stimulatory effect on human breast cancer cells in tissue culture. Estriol was also able to partially overcome the anti-estrogen effect of tamoxifen.[47]

While estriol appears to be safer than estrone and estradiol and, in some situations, provides some protection against carcinogenesis, it appears its use in breast cancer patients with active disease or with patients at high risk for breast cancer should be approached with caution. Further research, employing lower doses administered intermittently, rather than continuously, seems indicated.

Discussion

Estriol is a weak estrogen which is capable of exerting either antagonistic or agonistic effects depending on dosage size and schedule, and whether it is given alone or in conjunction with a stronger estrogen such as estradiol. It has been shown to be clinically effective for the treatment of menopausally-

related symptoms such as hot flashes, insomnia, and poor memory. In addition, postmenopausal conditions of vaginal atrophy with accompanying dryness, vaginal infections, and dyspareunia; and urinary tract changes resulting in recurrent UTIs, urgency, incontinence, and frequent urination are helped considerably with estriol, particularly when applied intravaginally.

Questions remain partially unanswered. Does estriol provide protection from osteoporosis and cardiac problems associated with the postmenopausal period? The studies conflict, with the most promising studies on both osteoporosis and cardiac risk prevention coming out of Japan. This appears to point to the possibility that dietary factors play a significant role; phytoestrogens from soy foods may act synergistically with estriol to provide protection. There is evidence progesterone is a bone-trophic hormone. Therefore, the addition of progesterone (not synthetic progestin which has many side-effects) for at least 10 or 15 days per month should provide extra protection from osteoporosis.

Although estriol appears to be much safer than estrone or estradiol, its continuous use in high doses may have a stimulatory effect on both breast and endometrial tissue. Therefore, it is advised to be used with caution in patients at risk for hormone-dependent cancers. Estriol appears more likely to contribute to proliferative changes when given orally in divided doses, resulting in sustained higher serum levels of the hormone, than when given once daily. However, the meta-analysis of its use intravaginally, which results in sustained levels of estriol, found no incidence of endometrial hyperplasia. The use of a natural progesterone for at least 10-14 days each month should eliminate some of the concern about possible endometrial build-up. The use of hormone therapies employing milder, lower dose hormones in forms identical to those produced by the human body rather than in synthetic forms which are not exact duplicates of hormones produced naturally, is an exciting area of study, begging for further research.

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