Estriol Summation Statement

Recently concerns have been raised as to the use of estriol for hormone replacement therapy. In an attempt to shed some light on the issue, we reviewed and analyzed more than 150 articles found via searches using PubMed and Medline OVID. Of these 150 articles, we then selected those we deemed most clinically relevant. The following chart is a summation of the data found within the 35 articles we felt most relevant to clinical practice concerning the safety and efficacy of estriol. It is not a comprehensive listing of available studies. The studies have been listed in reverse chronological order. Additionally, it is of note that a majority of the studies were conducted outside of the United States, particularly in Japan and Western Europe.

Articles included are those which show:

- Oral and vaginal estriol is not associated with increased risk of breast cancer
- Estriol is safe for use in postmenopausal women previously treated for breast cancer
- Estriol prevents bone loss and increases bone mineral density in postmenopausal women
- Oral estriol does not cause endometrial changes in postmenopausal women
- Estriol is effective in the treatment of atrophic vaginitis
- Estriol is safe and effective for the treatment of climacteric symptoms in postmeopausal women
- Vaginal application of estriol is systemically absorbed
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| 2006             | Lyytinen H, Pukkala E, Ylikorkala O. Breast Cancer Risk in Postmenopausal Women Using Estrogen-Only Therapy. Obstetrics & Gynecology 2006 Dec;108(6):1354-60. Finland and Germany study | Oral estriol or vaginal estrogens were not associated with a risk of breast cancer | o Cohort study  
 o Neither an oral estriol regimen nor vaginal use of any estrogen formulations were accompanied by a significantly increased risk of breast cancer.  
 o Oral Estriol used mainly for improving vaginal health  
 o Objective to evaluate whether the risk of estrogen-only therapy on breast cancer varies by dose, constituent, and route of administration  
 o Methods: All Finnish women older than age 50 years using oral or transdermal estradiol (n=84,729), oral estriol (n=7,941) or vaginal estrogens (n=18,314) for at least 6 months during 1994-2001 were identified from the national medical reimbursement register  
 o 2,857 patients from 1995-2001 taking Estriol for 6 months or more to less than 5 years had 34 observed cases of Breast Cancer out of 35 expected with a SIR of 0.98 and 95% CI of 0.68-1.37  
 o 3,717 patients form 1994-2001 taking Estriol for 6 months or more to less than 5 years had 88 observed cases of Breast Cancer out of 82 expected with a SIR of 1.07 and 95% CI of 0.86-1.32  
 o 1,367 patients took Estriol for 5 years or more with a total of 16 observed cases of breast cancer out of 11 expected with a SIR of 1.41 and 95% CI of 0.80-2.28  
 o Oral use of estriol did not increase the risk of breast cancer in this study |
 o Treatment groups (n=151):  
 Conjugated estrogens (CEE) 0.625 mg/day (n=35)  
 Estriol 2 mg/day (n=27)  
 Cyclic etidronate 200 mg/day for 2 weeks every 12 weeks (n=13)  
 Alendronate 5 mg/day (n=22)  
 Alfacalcidol 1 mg/day (n=23)  
 Menatetrenone 45 mg/day (n=5)  
 o Examined bone mineral density of the lumbar spine after 1 and 2 years of treatment |
## Estriol Research

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| 2006             | Continuation from: Terauchi M, Obayashi S, Aso T. Estriol, conjugated equine estrogens, and alendronate therapy for osteoporosis. Int J Gynaecol Obstet. 2006;92:141-2. Japan study | o Lumbar spine bone mineral density [baseline; % change at 1 yr (p value); % change at 2 yrs (p value)]:  
CEE: 0.82±0.1; 3.4±0.8 (0.0002); 4.7±1 (<0.0001)  
Estriol: 0.79±0.1; 2.5±0.8 (0.002); 3.3±0.8 (<0.0001)  
Etidronate: 0.79±0.1; 0.9±1 (0.14); 1.2±1.6 (0.04)  
Alendronate: 0.79±0.1; 2.9±0.7 (0.0003); 3.3±1.3 (0.0006)  
Alfacalcidol: 0.81±0.1; 0.1±0.8 (0.27); -0.1±1.2 (0.16)  
Menatetrenone: 0.82±0.1; -3.6±1.5 (0.17); -4.4±2.1 (0.25)  
Control: 0.84±0.1; -1.1±0.7; -2.1±0.8  
Significant increase in lumbar spine bone mineral density at both 1 and 2 years for CEE, estriol and alendronate  
Significant increase in lumbar spine bone mineral density only after 2 years for cyclical etidronate and control |  
| 2005             | Palacios S, Castelo-Branco C, Cancelo MJ, Vasquez F. Low-dose, vaginally administered estrogens may enhance local benefits of systemic therapy in the treatment of urogenital atrophy in postmenopausal women on hormone therapy. Maturitas.2005 Feb 14; 50(2):98-104. Spain study | Adding vaginal estriol to HRT may shorten the latency period for urinary symptoms | o Objective of study is to evaluate the effects of a combined therapy consisting of vaginal estriol with transdermal 17B-estradiol plus medroxyprogesterone acetate per os in shortening the period or urogenital symptoms  
o Randomized-double blind, controlled with placebo study  
27 women with climacteric symptoms and atrophic vaginitis were treated for 4 months with HT plus vaginal estriol 0.5 mg/day (group E) or placebo (group P)  
Local medication daily for the first 3 weeks and twice weekly thereafter.  
No differences on climacteric symptoms relief between the two groups (from 16.5+/−6.1 to 8.5+/−2.4 for E group and from 15.8+/−7.8 to 8.8+/−2.7 for P group; P<0.01 versus basal); However those women in group E reached significant improvement on urinary complaints since the first month of treatment.  
Papanicolaou smear showed reactive or reparative changes and karyophyphonotic index exhibited a significant increase in superficial cells in both groups and at the end of the study  
Investigators concluded adding vaginal estriol to HRT may shorten the latency period for urinary symptoms. |
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|                   |          | Vaginal estriol is safe for use up to 6 months following a TVT procedure | o 56 patients with stress urinary incontinence  
|                   | Italy study | | o Patients excluded if had endometrial thickness > 4 mm  
|                   | | | o All patients underwent tension-free vaginal tape (TVT) procedure then were randomly assigned to one of two groups (n=28 for each group):  
|                   | | | ET group – postoperative vaginal estrogen therapy  
|                   | | | Intravaginal estriol ovules 1 mg once daily for 1 month, then 2 ovules once weekly for 5 months as maintenance  
|                   | | | No ET group – no adjunctive estrogen therapy  
|                   | | | o AT 6 months, 53 of the 56 patients (95%) were successfully treated for stress urinary incontinence (no significant difference between groups)  
|                   | | | o Differences in urgency at 6 months:  
|                   | | | ET group – 4%  
|                   | | | No ET group – 29%  
|                   | | | p=0.01  
|                   | | | o TVT procedure seems to increase overactive bladder syndrome in postmenopausal patients  
|                   | | | o Vaginal estriol therapy significantly reduced the symptoms of urinary urgency, has a high rate of patient satisfaction and can be used by postmenopausal women for at least 6 months after TVT procedure |
|                   | France and Italy study | Weak estrogens (estriol) did not cause an increase in risk for breast cancer | o No significant increase in risk was observed in users of weak estrogens (oral estriol compounds or vaginally administered low-dose estrogens)  
|                   | | | o 7.1% utilized weak estrogens; 4.5% of patients used weak estrogens mainly with a mean duration of use for 2.1 years and standard deviation of 1.7  
|                   | | | o Age-adjusted RR (CI 95%) in patients taking the weak estrogens = 0.7 [0.4-1.3]  
|                   | | | o Multivariate adjusted RR(CI=95%) = 0.7 [0.4-1.2] |
## Estriol Research

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- Prospective, randomized, placebo-controlled study  
- 88 postmenopausal women with urogenital aging symptoms enrolled in study  
- Participants were randomly divided into 2 groups, with each group consisting of 44 women  
- Women in the treatment group received intravaginal estriol ovules: 1 ovule (1mg) once daily for 2 weeks and then 2 ovules once weekly for a total of 6 months as maintenance therapy  
- After therapy, symptoms and signs of urogenital atrophy significantly improved in the treatment group in comparison with the control group.  
- Thirty (68%) of the treated participants, and only 7 (16%) of the control participants registered a subjective improvement of their incontinence  
- In treated participants, we observed significant increases in mean maximum urethral pressure, in mean urethral closure pressure as well as in the abdominal pressure transmission ration to the proximal urethra  
- Our results show that intravaginal administration of estriol may represent a satisfactory therapeutic choice for those postmenopausal women with urogenital tract disturbances who have contraindications or refuse to undergo standard hormone therapy. |
| 2003             | Dew JE, Wren BG, Eden JA. A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer. Climacteric 2003;6:45-52. Australia study | Estriol safe for use in post-menopausal women previously treated for breast cancer | - Objective was to estimate the risk of recurrence of breast cancer associated with the use of topical vaginal estrogen therapy in the management of vaginal atrophy in women previously treated for breast cancer  
- Setting: 3 teaching hospitals in Sydney, Australia  
- 69 subjects elected to use topical vaginal estrogen therapy  
- Among the estrogen users, the median time interval from diagnosis to starting estrogen therapy was 5.25 years (range 0-20). Median time on therapy was 1 year.  
- 4 deaths among the vaginal estrogen users and 169 in the entire database; 6 tumor recurrences among the vaginal estrogen users & 330 in entire database  
- Limited systemic absorption has been reported with vaginal estriol suppositories or cream  
- Findings suggest topical use appears to be a safe form of hormone therapy for the patient population |
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<td>2002</td>
<td>Hayashi T, Kano H, Sumi D, Iguchi A, Ito I, Endo H. The long-term effect of estriol on endothelial function and bone mineral density in octogenarian women. JAGS. 2002 Apr;50(4):777-8.</td>
<td>Estriol increases bone mineral density</td>
<td>o 24 older women (mean age 80.3±3.5)  o Treatment group received 2 mg/day E3 for 110 weeks  o %FMD (percentage flow-mediated dilation) – measure of the changes in diameter of the right brachial artery to measure the effects on endothelial function  o %FMD in the E3 group was increased during the 110 week study period  o Serum concentrations of total cholesterol, triglycerides and apoproteins B100, C2, and E were unchanged in ALL patients  o HDL and apoprotein A1 significantly increased after 70 weeks of treatment in the E3 group  o BMD increased in E3 group and slightly decreased in control group (p&lt;0.05 for E3 group vs. control, and p&lt;0.05 in the E3 group for measurements at 30 weeks, 70 weeks, and 110 weeks vs baseline)  o Bleeding only occurred in 2 patients  o No other adverse effects observed  o E3 was well tolerated throughout the study  o Plasma levels of E3 and E2 were substantially increased  E2: baseline 4.6 pg/ml; 31.3±8.1 pg/ml  E3: baseline &lt; 5 pg/ml; 45.3±7.9 pg/ml</td>
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<td>2002</td>
<td>Kano H, Hayashi T, Sumi D, et al. Estriol retards and stabilizes atherosclerosis through an NO-mediated system. Life Sci. 2002 May 24;71(1):31-42.</td>
<td>Estriol possibly reduces the progression of atherosclerosis formation</td>
<td>o Evaluates the effects of E3 on the progression of atherosclerosis in a rabbit model  o 36 rabbits included and treated for 12 weeks  o 8 on high cholesterol diet (HCD) only (Gp I), 8 on HCD with 0.3mg/kg/day E3 (Gp II), 8 on HCD with 0.1mg/kg/day 17beta estradiol (E2) (Gp III), 8 non oophorectomized on HCD (GP IV), and 4 oophorectomized on regular diet (GP V)  o Neither E3 or E2 affected plasma lipid levels  o Changes in plasma E2 levels:  Gp II: baseline &lt; 5 pg/ml; 12 weeks 30.3±7.3 pg/ml  Gp III: baseline &lt; 5 pg/ml; 12 weeks 67.6±13.1 pg/ml  Gp IV: baseline 24.2±3.1 pg/ml; 12 weeks 22.3±6.8 pg/ml</td>
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| 2002             | Continuation from: Kano H, Hayashi T, Sumi D, et al. Estriol retards and stabilizes atherosclerosis through an NO-mediated system. Life Sci. 2002 May 24;71(1):31-42. | o Changes in plasma E3 levels: Gp II: baseline < 5 pg/ml; 12 weeks 60.9±13.0 pg/ml < 5 pg/ml throughout the study in the rest of the groups  
  o Area of atherosclerosis: Reduced by 60% in the E3 group  
  Reduced by 65% in the E2 group  
  Gp I surface involvement: 41.2±5.1%  
  Gp II surface involvement: 10.1±2.7%  
  Gp III surface involvement: 6.5±1.3%  
  o Anti-atherosclerotic effect of E3 comparable to that of 17β estradiol  
  o “E3 strongly activates NO-mediated systems and could play a role in retarding the progression of atherosclerosis and in stabilizing atheroma” | |
  o Multicenter, cross-sectional investigation  
  o 125 postmenopausal women who had been treated with either 1 or 2 mg oral estriol  
  o Control group of 116 postmenopausal women who had not received hormone replacement for at least a year  
  o Mean age in estriol group: 64.2±5.8 (range 55-76)  
  o Mean age in control group: 66.4±6.2 (range 55-79)  
  o Oral estriol group:  
    Mean estriol dose: 1.55 mg  
    Mean treatment duration: 4.3 years  
    Estriol prescribed for vaginal symptoms (72%) and/or urinary symptoms (48%) and/or other symptoms (3%)  
  o Histological evaluation only obtained for 201 women (other 40 women could not be obtained)  
  o Mean endometrial thickness in women with atrophic endometrium: Estriol group: 3±1.8 mm  
    Control group: 2.4±1.4 mm  
    p<0.01  
  o Mean endometrial thickness in ALL women: Estriol group: 3.7±2.83 mm (range 1-19 mm)  
    Control group: 2.5±1.75 mm (range 1-11mm) |
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<td>2002</td>
<td>Continuation from: Granberg S, Eurenius K, Lindgren R, Wilhelmsson L. The effects of oral estriol on the endometrium in postmenopausal women. Maturitas. 2002 Jun 25;42(2):149-56.</td>
<td>o Endometrial thickness in oral estriol group: ≤ 4 mm: 89% 5-7 mm: 10% ≥ 8 mm: 1%  o Endometrial thickness in control group: ≤ 4 mm: 97% 5-7 mm: 3% ≥ 8 mm: 0%  o Karyopycnotic Index (KPI) of the vaginal mucosa: Oral estriol group: 5.1±10.7 Control group: 0.7±2.8 (p&lt;0.0015)  o No clinically relevant difference found between the endometrium status of postmenopausal women on long-term oral estriol therapy and untreated controls</td>
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<td>2002</td>
<td>Sicotte NJ, Liva SM, Klutch R, et al. Treatment of Multiple Sclerosis with the Pregnancy Hormone Estriol. Ann. Neurol 2002;52:421-8. United States study</td>
<td>Estriol effective in treatment of MS in nonpregnant females o Crossover design study, 12 female patients with clinically definite Multiple Sclerosis: 6 with relapsing remitting MS and 6 with secondary progressive MS o All biopsies were negative for hyperplasia o Estriol was well tolerated by all patients with only menstrual abnormalities</td>
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<td>2001</td>
<td>Ishiko O, Hirai K, Sumi T, Tatsuta I, Ogita S. Hormone replacement therapy plus pelvic floor muscle exercise for postmenopausal stress incontinence. J Reprod. Med. 2001 Mar;46(3):213-20. Japan study</td>
<td>Combo therapy with estriol plus PFME was effective &amp; capable of serving as 1st line treatment for mild SI o Randomized, controlled trial o Use of Estriol in combination with pelvic floor muscle exercises (PFME) o Participants treated with a combination of estriol (1mg/day) and PFME (group A, n=32) and a group treated with PFME alone (group B, n=34) o Efficacy evaluated every 3 months based on stress scores obtained from a urinary incontinence questionnaire o Therapeutic effect in group A was more prominent for up to 18 months in mild UI and for up to 12 months in moderate UI</td>
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<td>2001</td>
<td>Yoshimura T, Okamura H. Short term oral estriol treatment restores normal premenopausal vaginal flora to elderly women. Maturitas. 2001 Sep 28;39(3):253-7. Japan study</td>
<td>Estriol is beneficial in the treatment of atrophic vaginitis o Objective: To determine the effects of oral estriol on vaginal flora and endometrial thickness o 59 postmenopausal women (age 50-75) with complaints of pruritus or vaginal discharge  All had been climacteric or amenorrheic for at least 18 months Had not had estrogens in the past 2 years  o Only enrolled if endometrial thickness &lt; 4 mm, as measured by transvaginal ultrasonography  o Oral estriol 2 mg for 14 days  o Collected samples of vaginal bacterial flora at baseline and after 14 days study period</td>
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Start of study: 6/59 subjects  
2 weeks: 27/59 (p<0.001)  
At start of study, there were no women in which lactobacillus was the only bacterium found  
After treatment, lactobacillus was the only bacterium found in 12 women (p<0.001) | o Lactobacilli:  
Start of study: 6/59 subjects  
2 weeks: 27/59 (p<0.001)  
At start of study, there were no women in which lactobacillus was the only bacterium found  
After treatment, lactobacillus was the only bacterium found in 12 women (p<0.001) |
Thus suitable for women who no longer want to experience uterine bleeding and those with a comparatively high risk of endometrial hyperplasia | o Objective of this study was to clarify the efficacy of estriol for estrogen replacement therapy in postmenopausal women with undefined symptoms and to evaluate endocrinological changes during therapy in relation to clinical outcome.  
o Administration of 2mg estriol in 168 postmenopausal patients was markedly effective in 22.6% of cases, effective in 45.2% fairly effective in 14.3% and ineffective in 17.9% of cases.  
o Menopause status was confirmed by the detection of postmenopausal levels of plasma follicle-stimulating hormone (FSH), luteinizing hormone (LH) and estradiol, i.e. an FSH level of at least 30mIU/ml, LH of at least 15mlU/ml and estradiol below 25 pg/ml.  
o Clinical evaluations were performed at the start of treatment (baseline) and after 2, 4, and 8 weeks of treatment.  
o Administration of estriol was markedly effectively in 22.6% (38/168) of cases, effective in 45.2% (76/168) and fairly effective in 14.3% (24/168)  
o Figure 1 shows that estriol was significantly more effective than placebo in reducing the score of the climacteric scale (2 weeks treatment, p<0.01; 8 weeks treatment, p<0.01)  
o For palpitations and muscular problems, improvement was observed in at least 80% of patients within 2 to 4 weeks.  
o For hot flashed, fatigue, insomnia, depression, and dizziness, improvement was observed in more than 70% of patients within 4 weeks |
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| 2001             | Continuation from:                                                       | o Estriol was significantly (p<0.001) more effective than placebo in reducing plasma FSH and LH levels at all three time points.  
 |                  | Ushiroyama T, Sakai M, Higashiyama T et al. Estrogen replacement therapy in postmenopausal women: a study of the efficacy of estriol and changes in plasma gonadotropin levels. Gynecol Endocrinol 2001;15:74-80. | o "The present results suggest that HRT using estiol has great potential for the alleviation of undefined symptoms of the menopause, and that the reduction of plasma gonadotropin levels is important in the management of patients undergoing HRT." |                                                                                                                                                                                                         |
 Japan study | o Objective: To assess the therapeutic efficacy and safety of oral estriol for the treatment of climacteric symptoms in postmenopausal women  
 o 68 postmenopausal women ages 35-62 (49.9±5.9)  
   35 of these women had undergone natural menopause (age 45-62)  
   33 of these women had undergone surgically induced menopause (age 35-54)  
 o None of the patients received HRT prior to study  
 o Oral estriol 2 mg/day for 12 months  
 o Unexpected bleeding in 14.3% of women who underwent natural menopause  
 o Other adverse effects: epigastralgia (2.9%), mastodynia (1.5%), palpitation (1.5%)  
 o Histologic evaluation of the endometrium after 12 months found no atypical endometrium in any women  
 o Ultrasound of the breast after 12 months found no tumor in all women  
 o Statistically significant changes in clinical characteristics:  
   Serum FSH: baseline 73.5±21.6; 12 months 65.8±28 (p<0.05)  
   Serum LH: baseline 29.9±10; 12 months 22±8.8 (p<0.01)  
 o Menopausal Index (MI): (subjective evaluation of menopausal symptoms)  
   Before: 29.3±14.4 points  
   End of 1st month: 39.1% reduction  
   12 months: 12.8±12.8 points (p<0.0001)  
 o Changes in MI for vasomotor symptoms: 75.8% reduction  
 o Changes in MI for psychological symptoms: 51.9% reduction  
 o Most significant reduction for hot flushes, night sweats and insomnia  
 o Self-assessed satisfaction with therapy:  
   End of 1st month: 72.1% satisfied  
   12 months: 84.2±11.4% satisfied (p<0.01) |
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<td>2000</td>
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<td>o 93.3% of women who completed the 12 month trial wished to continue therapy</td>
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<td>o Oral oestriol 2 mg daily for 12 months</td>
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<td>o After 12 months of treatment, no atypical endometrium in any of the patients in Group I Atrophic endometrium in 85.2% (23 patients) Weakly proliferative endometrium in 14.8% (4 patients)</td>
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<td>o No tumor found in any patients of either group on breast ultrasound</td>
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<td>o Subjective improvement of symptoms (index of Kupperman [KI]): KI scores prior to study were significantly increased: Group I – 17.8±6.7 Group II – 17.6±7.3</td>
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<td>% reduction in KI score at end of 1st month:</td>
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<td>Group I – 37.5% Group II – 28.8%</td>
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<td>% reduction in KI score at end of 3 months:</td>
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<td>Group I – 49.8% Group II – 56.8%</td>
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<td>Group II at the end of the 12 month study: KI score down to 3.6±3.1 (p&lt;0.01) % reduction in KI score from baseline – 80.4±20.2% (p&lt;0.01)</td>
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<td>Continuation of treatment after 3 months did not seem to induce any further substantial decreases in KI for Group I Significant difference in KI at the end of the study between the two groups (p&lt;0.05)</td>
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<td>2000</td>
<td>Continuation from: Takahashi K, Okada M, Ozaki T, et al. Safety and efficacy of oestriol for symptoms of natural or surgically induced menopause. Hum Reprod. 2000 May;15(5):1028-36.</td>
<td>o Patient satisfaction with therapy: At end of 1st month, about 75% in both groups At end of treatment: Group I – 85.2±8.4% Group II – 92.5±4.2% (p&lt;0.05) o Oestriol levels: Group I: pretreatment 13.9±11.7 pg/ml; 6 months 21.8±12.2 pg/ml; p&lt;0.01 12 months 17.1±7.4 pg/ml Group II: no statistically significant changes in levels throughout the study o FSH and LH: Group I: Baseline: FSH 94.8±37.8 mIU/l; LH 34.9±16.5 mIU/l 6 months: FSH 66.4±32.2; LH 23.7±13 (p&lt;0.01) 12 months: FSH 68.6±30.5; LH 25.4±11 Statistically significant decrease at 6 and 12 months Group II: Baseline: FSH 77.3±24.6; LH 26.3±11.2 12 months: FSH 59.6±15.7 (p&lt;0.01); LH 24.5±9.9 (p&lt;0.05) Statistically significant decrease at 12 months, but not 6 o No statistically significant differences from baseline in TG, HDL and LDL in either group o Histological evaluation of the endometrium in group I and ultrasound assessment of the breasts following 12 months of estriol treatment found normal results in all women o Adverse effects: Vaginal bleeding (group I), epigastralgia, mastodynia o No patients discontinued treatment due to side effects o Oral estriol appears to be safe and effective in relieving symptoms of menopausal women</td>
<td>210 non-obese, postmenopausal women aged &lt; 65 yrs with a normal mammogram at baseline o 7 treatment groups: (i) estradiol 2 mg (ii) estradiol 2 mg plus sequential medroxyprogesterone acetate (MPA) 5 mg days 10-16 of cycle (iii) estradiol 2 mg plus continuous MPA 2.5 mg (iv) combined equine estrogens (CEE) 0.625 mg (v) CEE plus sequential MPA 5 mg (vi) estriol 2 mg (vii) tibolone 2.5 mg</td>
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<td>2000</td>
<td>Valdivia I, Ortega D.  Mammographic density in postmenopausal women treated with tibolone, estriol or conventional hormone replacement therapy. Clin Drug Invest. 2000 Aug;20(2):101-7.</td>
<td>- Increased mammographic density occurred in 76 of the 210 patients receiving HRT (31.9%; 95% CI 25.7-38.6%)&lt;br&gt;- Increased mammographic density only occurred in one of the 30 control patients (3.3%; 95% CI 0-17.2%)&lt;br&gt;- Increases in mammographic density:&lt;br&gt;  - E2 group – 67% of patients&lt;br&gt;  - E2+MPA(s) group – 57% of patients&lt;br&gt;  - E2+MPA(c) group – 30% of patients&lt;br&gt;  - CEE group – 43% of patients&lt;br&gt;  - CEE+MPA(s) – 27% of patients&lt;br&gt;- No cases of increased mammographic density in estriol group (p&lt;0.05 when compared to each of the other HRT groups)&lt;br&gt;- Breast density actually decreased in 20% of the estriol patients (6 patients total)&lt;br&gt;- Conclusions:&lt;br&gt;  - Increased breast density occurred after treatment with HRT regimens containing estradiol or CEE&lt;br&gt;  - Increased breast density was more common in unopposed, rather than opposed, regimens</td>
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<tr>
<td>2000</td>
<td>Drew PD, Chavis JA. Female sex steroids: effects upon microglial cell activation. J Neuroimmunol 2000 Nov 1;111(1-2):77-85. United States study</td>
<td>Estriol use may contribute to the decreased severity of Multiple Sclerosis</td>
<td>- Study demonstrates that the female sex steroids estriol, beta-estradiol, and progesterone inhibit lipopolysaccharide (LPS) induction of nitric oxide production by primary rat microglia and by mouse N9 microglial line&lt;br&gt;- Estriol and progesterone, at concentrations with late pregnancy, inhibit NO and TNF-alpha production by activated microglia&lt;br&gt;- Evidence suggests that hormone inhibition of microglial cell activation may contribute to the decreased severity of multiple sclerosis symptoms commonly associated with pregnancy</td>
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<td>2000</td>
<td>Itoi H, Minakami H, Iwasaki R, Sato I. Comparison of the long-term effects of oral estriol with the effects of conjugated estrogen on serum lipid profile in early menopausal women. Maturitas. 2000;36:217-22. Japan study</td>
<td>Oral estriol does not increase total cholesterol or triglycerides</td>
<td>- Prospective study&lt;br&gt;- 67 women age 39-61 without climacteric symptoms&lt;br&gt;  - Intact uterus in 52 women (none w/ oophorectomy)&lt;br&gt;  - Perimenopausal status diagnosed based on absence of uterine bleeding for at least 6 months and FSH level &gt; 30 IU/L&lt;br&gt;  - Remaining 15 women had hysterectomy and bilateral oophorectomy for benign pelvic disease&lt;br&gt;- No patients had diabetes mellitus, hypertension, thromboembolic disease, history of cancer, other chronic illness&lt;br&gt;- Treatment period 48 months</td>
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<td>2000</td>
<td>Continuation from:</td>
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<td>o Three treatment groups:</td>
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<td>Itoi H, Minakami H, Iwasaki R, Sato I.</td>
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<td>Estriol 2 mg + medroxyprogesterone acetate 2.5 mg (n=21)</td>
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<td>Comparison of the long-term effects of oral estriol with the effects</td>
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<td>Conjugated estrogen 0.625 mg + medroxyprogesterone 2.5 mg (n=19)</td>
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<td>of conjugated estrogen on serum lipid profile in early</td>
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<td>1α-hydroxyvitamin D3 (n=12) or 1.8 g calcium lactate containing 250 mg elemental calcium (n=15) – Control group</td>
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<td>menopausal women. Maturitas. 2000;36:217-22.</td>
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<td>o No patients developed endometrial cancer during the study period</td>
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<td>o Total cholesterol:</td>
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<td>Control group – baseline 217.7±40.3; 48 months significant increase of 5.4±3.4%</td>
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<td>E3 group – baseline 216.3±34; 48 months significant decreased by 4.3±2.1%</td>
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<td>CE group – baseline 213.6±31.2; 48 months nonsignificant decrease of 1.9±2.1%</td>
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<td>o HDL cholesterol:</td>
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<td>Control group – baseline 59.6±12.5; 48 months decrease of 3.6±3%</td>
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<td>E3 group – baseline 63.3±16.9; 48 months nonsignificant increase of 3.8±3.3%</td>
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<td>CE group – baseline 69.3±12.4; 48 months significant increase by 10.7±2.4%</td>
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<td>At 48 months, HDL was significantly higher in E3 group than in control group (p&lt;0.05)</td>
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<td>o LDL cholesterol:</td>
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<td>Control group – baseline 138.2±37.7; 48 months significant increase of 11.8±6.3%</td>
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<td>E3 group – baseline 133.8±38; 48 months nonsignificant decrease of 5.2±3.6%</td>
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<td>CE group – baseline 127.7±28; 48 months significant decrease of 11.4±4%</td>
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<td>At 48 months, LDL was significantly lower in E3 group than in control group</td>
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<td>o Triglycerides:</td>
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<td>Control group – baseline 98.7±37.5; 48 months non statistically significant increase of 6.1±6.4%</td>
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<td>E3 group – baseline 96.4±37.6; 48 months non statistically significant decrease of 6.7±4.9%</td>
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<td>CE group – baseline 82.8±18; 48 months significant increase of 17.6±11.4%</td>
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Oral estriol may be an effective alternative for hormone replacement therapy in women with hypertriglyceridemia                                                                                                 |
Vaginal use administered low-potency oestrogen formulations was reported by 14.7% of cases and 11.3% of controls  
Post multivariate adjustment, the odds ratio associated with ever use was 1.2 and the increment per year of use was 2% (p=0.15).  
Exclusive use of vaginal low-potency oestrogen formulations was reported by 56 cases (6.9%) and 241 controls (6.8%), yielding and odds ration for every use of 1.4.  
No evidence of a differential effect of vaginal use of low potency oestrogen formulations on tumor grade or myometrial invasiveness.  
49% of vaginal treatment episodes consisted of oestriol (0.5mg), 44% dienostrol (0.5mg) and 7% oestradiol (25ug)                                                                                      |
2 groups: control group – 1 gm/day calcium lactate; study group – 1 gm/day calcium lactate + 2 mg/day estriol  
In each group some were “postmenopausal” (age 50-65) and some were “elderly” (age 70-84)  
Study lasted 10 months  
Effects on BMD:  
Postmenopausal E3 group – increase in BMD at 5 months 2.39%±9.03% and at 10 months 5.59%±4.79% (p<0.05)  
Postmenopausal Control group – slight, nonsignificant decrease -1.66%±2.5% at 5 months, -4.02%±7% at 10 months  
Postmenopausal women – significant difference in the rate of Increase in BMD after 10 months                                                                                                                  |
## Estriol Research

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| 1998             | Continuation from: Nishibe A, Morimoto S, Hirota K, et al. Comparison of effects of estriol on bone mineral density of vertebrae between elderly and postmenopausal women. J Bone Miner Metab. 1998;16:21-6. | Elderly E3 group – increase in BMD at 5 months 2.32%±4.47% and at 10 months 3.83%±7.9% (p<0.05) Elderly Control group – significant decrease at 5 months -2.5%±2.25% and at 10 months -3.26%±4.6% (p<0.05) Elderly women – significant difference in the rate of increase of BMD at both 5 and 10 months (p<0.01)  
  o No significant correlation between the age and rates of BMD increase  
  o Compression fracture did not occur in any patients  
  o No abnormal endometrial examinations  
  o Adverse effects in E3 groups: genital bleeding (24%) and epigastralgia (1%)  
  o Conclusions: “Hormone replacement with estriol is effective against degenerative osteoporosis, and that low-turnover bones in elderly women are also responsive to estriol” |                                                                                                                                           |
  o Open-label, randomized parallel group trial  
  o Purpose was to compare an estradiol ring (Estring®) and an estriol cream (Synapause®) regarding improvement of the patient’s subjective feeling of vaginal dryness  
  o Cross-over phase to determine product preference  
  o Each treatment period lasted 12 weeks  
  o Estradiol cream: 0.5 mg daily for the first 2 weeks, then maintenance dose of 0.5 mg three times a week  
  o Estradiol ring: constant release of about 7.5 mcg estradiol/24 hrs  
  o 165 patients participated  
  o Symptom of “feeling of vaginal dryness”  
    Intention to treat (ITT) analysis:  
    Ring: Symptom free 57%, Improved 25%, Unchanged 8%, Worse 0%, No data 10%  
    Cream: Symptom free 52%, Improved 27%, Unchanged 12%, Worse 2%  
    Per-Protocol (PP) analysis:  
    Ring: Symptom free 61%, Improved 29%, Unchanged 10%, Worse 0%  
    Cream: Symptom free 61%, Improved 23%, Unchanged 14%, Worse 3% |                                                                                                                                           |
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  Vaginal Dryness:  
  Ring: ITT – 57% cured (C), 25% improved (I); PP – 61% C, 29% I  
  Cream: ITT – 52% C, 27% I; PP – 61% C, 23% I  
  Pruritus vulvae:  
  Ring: ITT – 63% C, 20% I; PP – 65% C, 19% I  
  Cream: ITT – 55% C, 5% I; PP – 63% C, 3% I  
  Dyspareunia:  
  Ring: ITT – 50% C, 18% I; PP – 65% C, 26% I  
  Cream: ITT – 53% C, 27% I; PP – 65% C, 25% I  
  Dysuria:  
  Ring: ITT – 70% C, 0% I; PP – 73% C, 0% I  
  Cream: ITT – 60% C, 10% I; PP – 56% C, 13% I  
  Urinary urgency:  
  Ring: ITT – 57% C, 18% I; PP – 41% C, 18% I  
  Cream: ITT – 46% C, 26% I; PP – 47% C, 25% I  
  Only statistically significant difference seen in the symptom of pruritus vulvae – P=0.03 per ITT analysis  
  - 47% of patients treated with the vaginal ring selected “excellent” as an administration form as compared to only 6% using the cream  
  - 78% using the ring selected “good” or “excellent” as compared to only 40% for the cream – statistically significant (p<0.001)  
  - Preference:  
    64% preferred the ring  
    18% preferred the cream  
    5% had no preference  
    13% data not available  
  - Safety:  
    Both treatments were well tolerated. No difference seen in pts having minor vaginal irritation at baseline, 12 or 24 weeks. For both groups there was a reported improvement in irritation after either drug was started.  
  - Adverse effects – the frequency and kinds of adverse effects were the same in both the groups (bleeding, spotting, pruritus, urticaria) |
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|                  |                                                                           |                                                                                       | o Multicenter prospective open study  
|                  |                                                                           |                                                                                       | o 75 natural postmenopausal women with a bone mineral density (BMD) more than 10% below peak bone density  
|                  |                                                                           |                                                                                       | o Treated for 50 weeks with 2 mg/day estriol (E3) cyclically and 0.8 g/day calcium lactate continuously  
|                  |                                                                           |                                                                                       | o BMD increased by 1.79% (p<0.01 vs. pretreatment) after 50 weeks  
|                  |                                                                           |                                                                                       | o There was a decrease in biochemical markers of bone turnover  
|                  |                                                                           |                                                                                       | o Kupperman’s menopausal index (used to measure climacteric symptoms) improved after 5 weeks of treatment (p<0.01 vs. pretreatment)  
|                  |                                                                           |                                                                                       | o Genital bleeding only seen in 8% of patients  
|                  |                                                                           |                                                                                       | o “Endometrial histology and cytology showed neither abnormalities nor hyperplasia during and after the treatment”  
|                  |                                                                           |                                                                                       | o Investigators concluded that estriol demonstrated prevention of postmenopausal bone loss and improved climacteric symptoms effectively with low incidence of genital bleeding |
|                  |                                                                           |                                                                                       | o Inclusion into study were baseline and follow-up biopsies should be available, that patients be postmenopausal, and treated intravaginally  
|                  |                                                                           |                                                                                       | o All 337 postbaseline biopsies reported in the literature were classified as atrophic  
|                  |                                                                           |                                                                                       | o Study by Lauritzen gave a subgroup of patients 3mg/day estriol for 1 week (6 times recommended dose), did not induce endometrial proliferation  
<p>|                  |                                                                           |                                                                                       | o Study notes, no need to add sequential progestogens when using these preparations, not even for long-term treatment |</p>
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   - 80 women (ages 45-62) in natural or surgically-induced postmenopause for at least 60 months, not receiving hormone therapy for at least 3 months prior to admission  
   - 2 groups:  
     - Estriol vaginal suppository 0.5 mg/day for 28 days  
     - Estriol vaginal suppository 1 mg/day for 28 days  
   - Mean age 53.2±3.2 years  
   - Adverse effects:  
     - Local burning  
   - Clinical improvement:  
     - 0.5 mg group: 11/35 had > 75% improvement, 13/35 had 51-75% improvement, 9/35 had 25-50%, 2/35 had < 25%  
     - 1 mg group: 20/37 (> 75%), 15/37 (51-75%), 2/37 (25-50%), 0/37 (<25%)  
     - Both groups combined: 31/72 (>75%), 28/72 (51-75%), 11/72 (25-50%), 2/72 (<25%)  
   - Symptomatological scores:  
     - 50% improvement after 2 weeks (p<0.01), 67.7% improvement after 28 days (p<0.01) for both groups combined  
     - At 28 days, greater improvement in 1 mg group (p<0.05)  
     - 0.5 mg group: baseline 3.15±0.18; 28 days 0.18±0.07 (p=0.01)  
     - 1 mg group: baseline 2.86±0.17; 28 days 0.17±0.06 (p=0.01)  
   - Other parameters:  
     - Maturation Value:  
       - 0.5 mg: baseline 42.34±1.92; 28 days 73.49±1.86 (p=0.01)  
       - 1 mg: baseline 42.07±1.98; 28 days 73.78±1.9 (p=0.01)  
     - Kupperman Index:  
       - 0.5 mg: baseline 15.29±1.57; 28 days 6.89±0.87 (p<0.01)  
       - 1 mg: baseline 15.03±1.03; 28 days 4.27±0.57 (p<0.01)  
     - FSH (mu/ml):  
       - 0.5 mg: baseline 93.34±4.4; 28 days 68.15±0.87 (p=0.01)  
       - 1 mg: baseline 88.81±5.2; 28 days 62.09±4.58 (p=0.01)  
     - LH (mu/ml):  
       - 0.5 mg: baseline 32.86±2.58; 28 days 28.74±2.32 (p=0.01)  
       - 1 mg: baseline 35.33±2.6; 28 days 27.26±2.38 (p=0.01)  
   - Both doses showed significant improvement in urogenital symptoms  
   - Dose-related effect on climacteric complaints |
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| 1993             | Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. N Engl J Med. 1993 Sep 9;329:753-6. Israel study | Vaginal estriol is safe and effective for prevention of recurrent UTIs | o Randomized, double-blind, placebo-controlled trial  
o 93 postmenopausal women with a history of 3 or more microbiologically confirmed symptomatic episodes of urinary tract infection in the past year  
o Urine specimen taken for each patient before study entry to exclude current infection  
o Groups:  
  Estriol vaginal cream 0.5 mg each night for 2 weeks, then to be used twice weekly for 8 months (n=50)  
  Placebo cream used in the same manner (n=43)  
  Only 36 women in the estriol group and 24 in the placebo group completed the 8 month study  
  Reasons for withdrawal included local side effects, inadequate follow-up, death (due to MI), recurrent infection requiring chemophylaxis (10 patients all in placebo group)  
o Urinary tract infections per person year:  
  Estriol group – 0.5; Placebo group – 5.9; p<0.001  
  Kaplan-Meier analysis showed that the cumulative proportion of patients remaining free of UTI was significantly higher in the estriol group than in the placebo group (p<0.001 by the log-rank test)  
o Cumulative likelihood of remaining disease-free after 4 months:  
  Estriol group – 0.95 (95% CI 0.88-1)  
  Placebo group – 0.30 (95% CI 0.16-0.46)  
o Bacteriuria:  
  Estriol group – 12 episodes in 8 patients (10 symptomatic and 2 asymptomatic)  
  Placebo group – 111 episodes in 27 patients (103 symptomatic and 8 asymptomatic)  
  p<0.005  
o Number of days of antibiotic use:  
  Estriol group – 6.9±1.1  
  Placebo group – 32±7.8  
  p<0.001 |
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| 1993             | Continuation from: Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal  | o Lactobacilli vaginal cultures:  
Estriol group – pretreatment 0 lactobacilli cultures; after 1 month 22 (61%) lactobacilli cultures; after 8 months 21 (58%) lactobacilli cultures  
Placebo group – pretreatment 0 lactobacilli cultures; after 1 month 0 lactobacilli cultures (p<0.001 compared to estriol group); after 8 months 0 lactobacilli cultures (p<0.001 compared to estriol group)  
Placebo group – pretreatment 0 lactobacilli cultures; after 8 months 0 lactobacilli cultures (p<0.001 compared to estriol group)  
Placebo group – pretreatment 0 lactobacilli cultures; after 8 months 0 lactobacilli cultures (p<0.001 compared to estriol group)  
Estriol group – pretreatment 24 (67%) cultures; after 1 month 11 (31%) cultures; after 8 months 10 (28%) cultures  
Placebo group – pretreatment 16 (67%) cultures; after 1 month 15 (63%) cultures (p<0.005 compared to estriol group); after 8 months 17 (71%) cultures (p<0.005 compared to estriol group)  
No significant change in cultures for placebo group, while it was reduced in estriol group  
Vaginal pH:  
Estriol group – pretreatment 5.5±0.7; after 1 month 3.7±0.8; after 8 months 3.6±1  
Placebo group – pretreatment 5.8±1.2; after 1 month 6.2±1.2; after 8 months 6.1±2 (p<0.001 at 1 and 8 months when compared to estriol group)  
Appeared to be a relation between vaginal-colonization status and risk of infection  
Lactobacillus – 3 of 23 women in estriol group colonized and 7 of 13 not colonized developed UTI  
Enterobacteriaceae – 28 women colonized in both groups, 7 of the 10 in estriol group and 14 of 18 in placebo group had UTIs  
Localized adverse reactions: vaginal irritation, burning and itching occurred in 10 estriol treated women and 4 in placebo group  
Investigators concluded that intravaginal estriol prevents recurrent urinary tract infections, probably through modification of the vaginal flora.  |
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  o 80 postmenopausal women (age 57-65)  
    Only 60% (48 patients) completed the 10 year study  
  o In menopause for 5-15 years (mean 9.1 yrs)  
  o All subjects had symptoms of vaginal atrophy, urinary incontinence or recurrent urinary tract infections  
  o None had estrogen replacement therapy previously  
  o Vaginal estriol suppository 0.5 mg every evening for 2 weeks, then twice a week thereafter for 1 to 10 years  
  o Adverse effects reported: pruritus, local irritation, vaginal pain  
  o Bacteria in the urine:  
    At start, 40% had significant bacteria in their urine (E coli and Proteus)  
    At end of study, only 5 women had bacteria (E coli)  
  o Patients with sensory urge incontinence (15 patients) reported decreased frequency and urgency of symptoms and rare nocturia  
  o Of patients with stress incontinence, 30 out of 40 reported improvement or cure of incontinence  
    The other 10 reported no improvement  
    No statistically significant improvement in urethral closure pressure, change in functional urethral length  
    Statistically significant increase in abdominal pressure transmission to the proximal urethra during cough pressure profile measurement  
    Before treatment: 70±22; After treatment: 106±15 (p<0.01)  
  o Moderate to severe atrophic vaginitis disappeared in 79% of cases after 16 weeks and 98% after 12 months  
  o None of the patients had suspicious or positive cervical smears during treatment  
  o Endometrial biopsies obtained from 48 patients after 8 to 10 years of treatment and only 7 showed weakly proliferative changes (none being atypical) |
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 o Estradiol used in 56% of pts, conjugated estrogens in 22%, and estriol in 22%  
 o Estradiol associated with a 1.8 fold increase in risk of breast cancer with more than 6 years of treatment (95% CI 0.7 to 4.6)  
 o Relative risk for conjugated estrogens was 1.1 (95% CI 0.9 to 1.5) – no increase in risk seen  
 o Relative risk for “other estrogens” (mainly estriol) was 1.0 (95% CI 0.8-1.3) – no increase in risk seen  
 o Relative risk for > 6 years of combination estrogen and progestin therapy 4.4 (95% CI 0.9-22.4)  
 o Conclusions: “Long-term perimenopausal treatment with estrogens (or at least estradiol compounds) seems to be associated with slightly increased risk of breast cancer, which is not prevented and may even be increased by the addition of progestins.” |
| 1989             | van Haaften M, Donker GH, Haspels AA, et al. Oestrogen concentration in plasma, endometrium, myometrium and vagina of postmenopausal women, and effects of vaginal oestriol (E3) and oestradiol (E2) applications. J. Steroid Biochem. 1989 Apr; 33(4A):647-653. The Netherlands study | Estriol when given vaginally produces a prolonged plasma E3 concentration | o Goal was to investigate the differences in uptake and retention of E2 and E3, we set up a study in which postmenopausal women were treated with daily vaginal applications of E2 or E3  
 o 29 postmenopausal women who had to undergo a hysterectomy for prolapsus uteri or uterus myomatosus and not for oncological reasons participated in this study (age between 49 and 82 yo, BMI between 20-35).  
 o Participants divided into 3 groups: I-a control group of untreated women (group C, n=12), II women who were treated for three weeks with vaginally applied E3, 0.5mg/day (group E3, n=8), and III women with vaginally applied E2, 0.05mg/day (group E2, n=9)  
 o Hormones were administered every evening in ovula  
 o Investigators conclude that there is no difference at this pharmacological level of mechanism of action (tissue uptake and retention of the hormones) between the human vagina and uterus, which may help answer why E3 has a specific vaginotrophic, non-uterotrophic effect contrary to E2.  
 o Vaginal E3 treatment produced a prolonged (at least 12h) elevation of the plasma E3 concentration |
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| 1985             | Blum M. Benefits of vaginal estriol cream combined with clonidine HCL for menopausal syndrome treatment. Clin Edp Obst Gynecol. 1985;12(1-2):1-2. Israel study | Estriol does not induce endometrial proliferation or breakthrough bleeding; can be recommended for post menopausal syndrome | o Objective to show the benefits of an Estriol vaginal cream, as a restorer of normal psychological and sexual life, without disturbing basic metabolism, but preventing osteoporosis  
  o 25 postmenopausal women mean age of 57.2 years, treatment with Estriol vaginal cream (Ovestin) gives rise to (but within normal limits) to cholesterol, triglycerides and HDL – cholesterol.  
  o 25 mg Clonnirit (Clonidine HCL from Rafa- Jerusalem) tablets given BID to the topical Estriol vaginal treatment, was able to relieve hot flushes, profuse sweating and sleep disturbances.  
  o Urinary Calcium Creatinine ratio, a clear lowering from 0.25 +/- 0.09 before to 0.19 +/-0.08 during 4 months of treatment, statistically significant, T=35.5, P<0.01. They conclude that "vaginal estriol cream was able to stop calcium loss and prevent osteoporosis.  
  o No contraindications were shown |
| 1982             | Trevoux R, van der Velden WH, Popovic D. Ovestin vaginal cream and suppositories for the treatment of menopausal vaginal atrophy. Reproduccion. 1982 Apr-Jun;6(2):101-6. France, The Netherlands and Yugoslavia study | Vaginal estriol is effective in the treatment of post menopausal vaginal atrophy. Vaginal estriol is absorbed | o 82 postmenopausal or ovariectomized women (age 36-79), presenting with vaginal atrophy or related symptoms  
  o 2 groups:  
    Ovestin vaginal cream (n=54) – 0.5 mg estriol  
    Ovestin vaginal suppositories (n=28) – 0.5 mg estriol  
  o Used 0.5 mg every night for 3 weeks (either cream or suppository) then used maintenance dose of 0.5 mg only twice weekly  
  o Mean plasma E3 levels following administration of cream:  
    Baseline: undetectable (< 12 pg/ml)  
    1 hr: 113.5±10 pg/ml (mean±SD)  
    2 hr: 98.6±11 pg/ml  
    4 hr: 74±9 pg/ml  
    6 hr: 54.7±12.1 pg/ml  
    8 hr: 34.6±7.7 pg/ml  
  o Chance in maturation value (MV):  
    Cream: baseline 44.5; 3 weeks 73.8  
    Suppositories: baseline 39.1; 3 weeks 69.8  
    MV unchanged during twice weekly maintenance therapy  
  o Dyspareunia and vaginal dryness was improved in all patients presenting with the compliant  
  o Subepithelial petechiae disappeared completely and mucosa had normal appearance  
  o Endometrium remained atrophic in the 15 patients examined  
  o Both treatments well tolerated and patients satisfied with treatment Conclusions: 0.5 mg E3 twice weekly is an effective maintenance dose for the treatment of vaginal atrophy |
## Estriol Research

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  o Each subject received one vaginal suppository per day containing 0.5mg estriol dissolved in Witepsol for a period of 10 days  
  o Blood was drawn from a cubital vein immediately before and 1,2,4, and 8h after the beginning of treatment.  
  o Total serum estrone, 17B estradiol, estriol, FSH, LH, and prolactin were estimated in duplicate by radioimmunoassay.  
  o In all subjects there was a very impressive rise of circulating total estriol from 35-70 (mean 50) pg/ml to 500-1950 (mean 1290) pg/ml within the first hour.  
  o Estrogen mean maximal increase was 3310% within 1 – 2 hours; pretreatment levels were again reached 8h later.  
  o Repeated intra-vaginal application of estriol resulted in a significant rise of the mean serum estriol levels while the other estrogens remained unchanged.  
  o It was concluded that intra-vaginal application of estriol is a most suitable local and systemic estrogen replacement therapy, which is more effective than the oral regimen  
  o Englund and Johansson applied 6 and 12 mg of estriol; the peak values of unconjugated serum levels were 80-200 and 150-490 pg/ml, respectively, after 1 hour. The pre-treatment levels of 30pg/ml were reached again within 3h.  
  o “From the physiological point of view the intra-vaginal route seems therefore to provide a more consistent pattern.” |
  o Treatment groups:  
    - Group A – Ovestin vaginal cream 1 mg/day E3  
    - Group B – Ovestin vaginal cream 0.5 mg/day E3  
    - Group C – Ovestin vaginal suppositories 0.5 mg/day E3  
  o “Vaginal smears showed a marked shift from an atrophic picture to the kind of picture seen at midcycle in eugonadal women at the end of the period of daily treatment. This effect persisted during maintenance therapy”  
  o Mean E3 levels – sharp rise on day 1 from undetectable (E3<12 pg/ml)  
    - Group A – 123.6 pg/ml at 1 hr  
    - Group B – 110.8 pg/ml at 1 hr  
    - Gradual decline over the next 5 hours |
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<td>1980</td>
<td>Continuation from: Kicovic PM, Cortes-Prieto J, Milojevic S, Haspels AA, Aljinovic A. The treatment of postmenopausal vaginal atrophy with Ovestin vaginal cream or suppositories: clinical, endocrinological and safety aspects. Maturitas. 1980 Dec;2(4):275-82.</td>
<td>o On day 21, plasma E3 level at 0 h (approximately 12 hours after last dose) around 26 pg/ml, rising to mean peaks of: Group A – 104.9 pg/ml at 1 hr Group B – 95 pg/ml at 1 hr o Plasma E2 and E1 levels on days 1 and 21 were unaffected in both group A and group B after E3 administration o In group A, FSH and LH were slightly suppressed on day 21 as compared to day 1 (FSH 11.8% suppression, LH 18.5% reduction) – not clinically significant; less pronounced in group B o No change in Prolactin or sex hormone binding globulin o Vaginal suppository: E3 levels rose from undetectable (&lt; 12 pg/ml) to a mean peak of 92.6 pg/ml on day 1 and from 30.8 pg/ml to a mean peak of 92.8 pg/ml on day 15 (2 hr after administration) E1 and E2 levels unchanged Slight gonadotrophin suppression o After 2-3 weeks of therapy, pallor, petechiae, friability, and tenderness resolved, dyspareunia was cured, and normal appearance of the vaginal mucosa was reestablished o The 0.5 mg/day dose was as effective as the 1 mg/day dose; no difference between cream and suppositories with respect to efficacy or acceptability o Maintenance doses (twice weekly) were sufficient to maintain benefit o No side effects reported</td>
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<td>1980</td>
<td>Schiff I, Tulchinsky D, Ryan KJ, et al. Plasma estiol and its conjugates following oral and vaginal administration of estriol to postmenopausal women: Correlations with Gonadotropin levels. Am. J Obstetrics &amp; Gynecology. 1980 Dec 15; 138(8): 1137-41. United States study</td>
<td>Larger doses of estriol can be absorbed orally than vaginally o 6 hypogonadal women studied to compare the metabolic fate and the biologic effects of 4mg of estriol administered orally or vaginally to these postmenopausal women o Each patient was studied twice, once after receiving 4mg of E3 orally and again, 4 weeks later, after having 4mg of E3 dispensed in 2ml of saline, placed in the vagina o Study confirms E3’s biologic activity in women by the noted increase in LH that followed vaginal E3 admin o Total E3 plasma concentration in blood was higher after oral than after vaginal admin (15 to 64 versus 1.0 to 3.0 ng/ml)</td>
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<td>1978</td>
<td>Schiff I, Wentworth B, Koos B, Ryan K, Tulchinsky D. Effect of estriol administration on the hypogonadal woman. Fertility and Sterility 1978 Sep;30(9):278-82. United States study</td>
<td>Biological effects of estriol Conjugation of estriol given vaginally is less rapid than in oral administration</td>
<td>o 14 hypogonadal women received either vaginal or oral estriol o 0.5mg admin vaginally to 5 patients resulted in increases of serum unconjugated and conjugated estriol levels which were maximal at 1 and 2 hours following treatment (161+/- 59 pg/ml and 762 +/- 146 pg/ml, respectively) o Ingestion of 8mg of estriol orally caused a minimal increase in the serum unconjugated estriol concentration (from 0.1+/- 0.01 ng/ml to 62.4 +/- 13.8ng/ml) o Shift to the right in the vaginal maturation index (P&lt;0.05) was noted at the end of the treatment course and suggested an estrogenic effect on the vaginal epithelium o Estriol admin vaginally is rendered more potent due to it being conjugated at a less rapid rate than via oral admin</td>
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