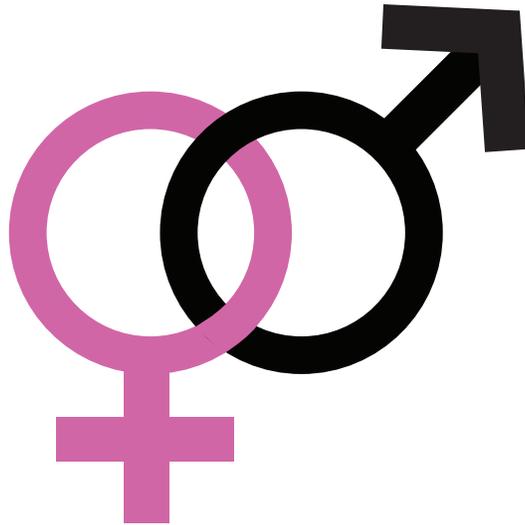




Women's International Pharmacy
Custom Compounded Prescriptions for Men and Women

Bioidentical Hormone Abstracts for Women



Women's International Pharmacy compiled abstracts of the most up to date scientific literature on biologically identical hormones for female hormonal health concerns. To obtain the full-text of any of the abstracts listed, please refer to your local medical library or online source.

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Progesterone

Brain

Neurology. 1995; 45: 1660-1662.

Progesterone therapy in women with complex partial and secondary generalized seizures.

Herzog, A.G., M.D., MSc.

This open trial assessed the effects of adjunctive progesterone therapy on seizure frequency in 25 women with catamenial exacerbation of complex partial (CPS) and secondary generalized motor (SGMS) seizures. Progesterone was well tolerated by 23 of the 25 women and had readily reversible dose-related side effects of asthenia and emotional depression in two. Eighteen women (72%) experienced a decline in seizure frequency during a 3-month treatment period compared with the 3 months prior to therapy (p less than 0.01). Average daily CPS frequency declined by 54% (p less than 0.01), SGMS by 58% (p less than 0.02).

Ann Emerg Med. 2007; 49: 391-402.

ProTECT: A Randomized Clinical Trial of Progesterone for Acute Traumatic Brain Injury.

Wright, D., et al.

Study objective: Laboratory evidence indicates that progesterone has potent neuroprotective effects. We conducted a pilot clinical trial to assess the safety and potential benefit of administering progesterone to patients with acute traumatic brain injury.

Methods: This phase II, randomized, double-blind, placebo-controlled trial was conducted at an urban Level I trauma center. One hundred adult trauma patients who arrived within 11 hours of injury with a postresuscitation Glasgow Coma Scale score of 4 to 12 were enrolled with proxy consent. Subjects were randomized on a 4:1 basis to receive either intravenous progesterone or placebo. Blinded observers assessed patients daily for the occurrence of adverse events and signs of recovery. Neurologic outcome was assessed 30 days postinjury. The primary safety measures were differences in adverse event rates and 30-day mortality. The primary measure of benefit was the dichotomized Glasgow Outcome Scale–Extended 30 days postinjury.

Results: Seventy-seven patients received progesterone; 23 received placebo. The groups had similar demographic and clinical characteristics. Laboratory and physiologic characteristics were similar at enrollment and throughout treatment. No serious adverse events were attributed to progesterone. Adverse and serious adverse event rates were similar in both groups, except that patients randomized to progesterone had a lower 30-day mortality rate than controls (rate ratio 0.43; 95% confidence interval 0.18 to 0.99). Thirty days postinjury, the majority of severe traumatic brain injury survivors in both groups had relatively poor Glasgow Outcome Scale–Extended and Disability Rating Scale scores. However, moderate traumatic brain injury survivors who received progesterone were more likely to have a moderate to good outcome than those randomized to placebo.

Conclusion: In this small study, progesterone caused no discernible harm and showed possible signs of benefit.

Breast

Br J Cancer. 1996; 73: 1552-1555.

Serum progesterone and prognosis in operable breast cancer.

Mohr, P.E., Wang, D.Y., et. al.

Several studies have now shown that women with operable breast cancer undergoing tumour excision during the luteal phase of the menstrual cycle have a better prognosis than those having surgery during the follicular phase. As part of a prospective study of prognostic factors in breast cancer, blood was taken at the time of surgery. Between 1975 and 1992 this was available from 289 premenopausal women within 3 days of tumour excision. All were treated by either modified radical mastectomy or breast conservation including axillary clearance and the date of last menstrual period (LMP) was known in 239 (80%) cases. Blood samples were assayed for both oestradiol (E2) and progesterone (P). Because of the wide inter-individual variation in E2 levels there was no clear relationship between E2 and LMP. However, using a running mean smoothing technique the expected cyclical variation could be discerned. There was no significant association between E2 and survival. Smoothing of the P data yielded a pattern similar to the normal hormone profile. Those cases with a progesterone level of 4 ng ml⁻¹ or more had a significantly better survival than those with a level of <4 ng ml⁻¹. This was especially clear in node-positive patients ($P < 0.01$). The possibility of misclassification of menstrual cycle status because of misreported LMP has been minimized by applying independent hormonal measurements (P) of cycle activity. This parameter will also identify women who may be undergoing anovular cycles. Thus this study has confirmed that a raised level of progesterone at the time of tumour excision is associated with and improvement in prognosis for women with operable breast cancer.

Int J Cancer. 2005; 114: 448-454.

Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort.

Fournier, A., et al.

Most epidemiological studies have shown an increase in breast cancer risk related to hormone replacement therapy (HRT) use. A recent large cohort study showed effects of similar magnitude for different types of progestogens and for different routes of administration of estrogens evaluated. Further investigation of these issues is of importance. We assessed the risk of breast cancer associated with HRT use in 54,548 postmenopausal women who had never taken any HRT 1 year before entering the E3N-EPIC cohort study (mean age at inclusion: 52.8 years); 948 primary invasive breast cancers were diagnosed during follow-up (mean duration: 5.8 years). Data were analyzed using multivariate Cox proportional hazards models. In this cohort where the mean duration of HRT use was 2.8 years, an increased risk in HRT users compared to nonusers was found (relative risk (RR) 1.2 [95% confidence interval 1.1–1.4]). The RR was 1.1 [0.8–1.6] for estrogens used alone and 1.3 [1.1–1.5] when used in combination with oral progestogens. The risk was significantly greater ($p < 0.001$) with HRT containing synthetic progestins than with HRT containing micronized progesterone, the RRs being 1.4 [1.2–1.7] and 0.9 [0.7–1.2], respectively. When combined with synthetic progestins, both oral and transdermal/percutaneous estrogens use were associated with a significantly increased risk; for transdermal/percutaneous estrogens, this was the case even when exposure was less than 2 years. Our results suggest that, when combined with synthetic progestins, even short-term use of estrogens may increase breast cancer risk. Micronized progesterone may be preferred to synthetic progestins in short-term HRT. This finding needs further investigation.

Breast Cancer Res Treat. 2007; 101: 125-134.

Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys.

Wood, C., et al.

The addition of the synthetic progestin medroxyprogesterone acetate (MPA) to postmenopausal estrogen therapy significantly increases breast cancer risk. Whether this adverse effect is specific to MPA or characteristic of all progestogens is not known. The goal of this study was to compare the effects of oral estradiol (E2) given with either MPA or micronized progesterone (P4) on risk biomarkers for breast cancer in a postmenopausal primate model. For this randomized crossover trial, twenty-six ovariectomized adult female cynomolgus macaques were divided into social groups and rotated randomly through the following treatments (expressed as equivalent doses for women): (1) placebo; (2) E2 (1 mg/day); (3) E2 + P4 (200 mg/day); and (4) E2 + MPA (2.5 mg/ day). Hormones were administered orally, and all animals were individually dosed. Treatments lasted two months and were separated by a one-month washout period. The main outcome measure was breast epithelial proliferation, as measured by Ki67 expression. Compared to placebo, E2 + MPA resulted in significantly greater breast proliferation in lobular ($P < 0.01$) and ductal ($P < 0.01$) epithelium, while E2 + P4 did not. Intramammary gene expression of the proliferation markers Ki67 and cyclin B1 was also higher after treatment with E2 + MPA ($P < 0.01$) but not E2 + P4. Both progestogens significantly attenuated E2 effects on body weight, endometrium, and the TFF1 marker of estrogen receptor activity in the breast. These findings suggest that oral micronized progesterone has a more favorable effect on risk biomarkers for postmenopausal breast cancer than medroxyprogesterone acetate.

Cardiovascular

Arterioscler Thromb Vasc Biol. 2004; 24: 955-961.

Prevention of Coronary Hyperreactivity in Preatherogenic Menopausal Rhesus Monkeys by Transdermal Progesterone.

Hermesmeyer, R.K., et al.

Objective: To test if transdermal progesterone (P) confers coronary vascular protection in surgically menopausal preatherosclerotic rhesus monkeys.

Methods and Results: Ovariectomized rhesus monkeys fed an atherogenic diet (AD) for 19 months were treated with an investigational transdermal P cream (n_7) or identical placebo cream (n_5) for 4 weeks. Aorta and carotids showed fatty streaks and Oil Red O staining demonstrated lipid deposition. Serum P levels in P-treated rhesus monkeys (0.6 ng/mL) were significantly greater than placebo (0.2 ng/mL). Significant elevation of cholesterol, LDL cholesterol, and HDL cholesterol, was noted in all animals. Lp(a) was significantly attenuated in the AD-fed P-treated monkeys. Coronary angiographic experiments stimulating vasoconstriction by intracoronary injections of serotonin plus U46619 showed exaggerated prolonged actions amplified by AD, but significant protection against severe prolonged vasoconstriction in P-treated monkeys. Immunocytochemistry confirmed co-expression of P and thromboxane prostanoid (TP) receptors in coronaries and aorta. Western blotting demonstrated TP receptor attenuation in vascular muscle after P treatment.

Conclusions: Coronary hyperreactivity, a putative component of coronary artery disease mediated via increased vascular muscle thromboxane prostanoid receptors, can be prevented by subphysiological levels of P, not only in nonatherosclerotic (previously shown) but also in preatherosclerotic primates.

Blood (ASH Annual Meeting Abstracts). 2004; 104: Abstract 5317.

Topical Progesterone Cream Does Not Increase Thrombotic and Inflammatory Factors in Postmenopausal Women

Stephenson, K., Price, C., et al.

Postmenopausal women have an increased risk of cardiovascular disease, and heart disease is the leading cause of death in postmenopausal American women. Conventional hormone replacement therapy has been shown to result in an increase in thrombotic events in large prospective clinical trials including HERS I, and the recently halted Women's Health Initiative. One possible mechanism for this observed increase is the unfavorable net effects of conjugated equine estrogens and medroxyprogesterone acetate on the hemostatic balance and inflammatory factors. An estimated 50 million American women are peri or postmenopausal and clinical therapies for menopausal symptoms remain a significant challenge in light of the known thrombotic risks. In this prospective blinded study, we examined the short-term effect of topical progesterone cream on menopausal symptom relief in 30 healthy postmenopausal women. Potential adverse effects of topical progesterone on hemostatic and inflammatory factors and cortisol levels were also examined. Subjects were randomized to first receive either 20 mg of topical progesterone cream or placebo cream for 4 weeks. Following a subsequent 4 week washout period, subjects were crossed over to either placebo cream or active drug for an additional 4 week period. In each case, progesterone and cortisol levels were monitored by salivary sampling. Baseline values, 4 week follow-up values and end-of-study values were also obtained for the Greene Climacteric Scale, total factor VII:C, factor VIIa, factor V, fibrinogen, antithrombin, PAI-I, CRP, TNF α , and IL-6. For subjects receiving 20 mg of topical progesterone cream for 4 weeks, Greene Climacteric Scale scores were consistently and significantly improved (decreased) over baseline, demonstrating significant relief from menopausal symptoms. In addition, in a subpopulation of hypercortisolemic women, topical progesterone was associated with a favorable decrease in nocturnal cortisol. Surprisingly, and in sharp contrast to earlier studies with conventional hormone replacement therapy, topical progesterone had no effect on any of the hemostatic components examined: total factor VII:C, factor VIIa, factor V, fibrinogen, antithrombin, and PAI-1 levels were all unchanged. Levels of CRP, TNF α , and IL-6 also remained unchanged. From this study we conclude that administration of topical progesterone cream at a daily dose of 20 mg significantly relieves menopausal symptoms in postmenopausal women without adversely altering prothrombotic potential. Since the thrombotic complications that are typically observed with conventional hormone replacement therapy do not seem to occur with topical progesterone, this treatment should be seriously considered as an effective and safe alternative clinical therapy for women suffering from menopausal symptoms.

Br Med J. 1985; 290: 13.

Natural progesterone and antihypertensive action

Rylance, P.B., Brincat, M.

In a placebo controlled, double blind crossover study natural progesterone was given by mouth, in increasing doses, to six men and four postmenopausal women with mild to moderate hypertension who were not receiving any other antihypertensive drugs. When compared with values recorded before treatment and during administration of placebo progesterone caused a significant reduction in blood pressure, suggesting that progesterone has an antihypertensive action rather than a hypertensive one as has been previously thought. This possible protective effect of progesterone should be investigated further.

General

Fertil Steril. September 1999; 72 (3): 389-397.

Micronized Progesterone: Clinical Indications and Comparison with Current Treatments.

Fitzpatrick, L.A., M.D., Good, A., M.D.

Objective: To integrate and evaluate the pharmacokinetic, endocrine, and clinical effects of micronized progesterone formulations.

Design: Published articles concerning the pharmacokinetics of orally administered progesterone and the potential clinical uses of oral micronized progesterone were reviewed. Results concerning their use for secondary amenorrhea, premenopausal bleeding disorders, luteal phase dysfunction, termination of premature labor, hormone replacement therapy, and premenopausal syndrome are summarized. Critical issues to be resolved through ongoing preclinical and clinical research are highlighted.

Result(s): Because of the enhanced bioavailability of oral micronized progesterone, the compound may be useful for a variety of therapeutic indications. Oral micronized progesterone is available in France, and a formulation recently has been approved in the United States for the treatment of secondary amenorrhea and postmenopausal hormone replacement therapy. A large body of evidence, including the Postmenopausal Estrogen/Progestin Interventions study, suggests that the use of a combination of estrogen and oral micronized progesterone is optimal for long-term hormone replacement therapy. There also are data indicating that oral micronized progesterone could be of potential use for the treatment of premenopausal bleeding disorders, luteal phase disorders, and premature labor.

Conclusion(s): Oral micronized progesterone has widespread clinical potential, particularly for the treatment of secondary amenorrhea and dysfunctional premenopausal bleeding, and as a component of postmenopausal hormone replacement therapy.

Clin Obstet Gynecol. December 1995; 38 (4): 902-914.

Micronized Progesterone: Vaginal and Oral Uses.

Simon, J.A., M.D.

In this review, the focus is on oral micronized progesterone and its uses in real and presumed progesterone deficiency disorders. A special emphasis on clinical pharmacokinetics and comparison with other progesterone dosage forms (e.g., vaginal, intramuscular, sublingual) is included to sensitize the reader to the potential for the highly variable absorption and possibly clinical efficacy. First, however, a short introduction to pharmacokinetics and review of progesterone's endocrinology and metabolism will be completed.

J Womens Health Gend Based Med. 2001; 10 (10): 991-997.

Natural Vaginal Progesterone is Associated with Minimal Psychological Side Effects: A Preliminary Study.

Shantha, S., M.D., Brooks-Gunn, J., Ph.D., et al.

The objective of this study was to evaluate the psychological side effects of a transvaginal natural progesterone gel in hormone replacement therapy (HRT). This 3-month preliminary study was part of a multicenter study previously performed in our center. We enrolled 49 women (ages 18–45 years) with hypothalamic amenorrhea (HA) ($n = 40$) and premature ovarian failure (POF) ($n = 9$). Estrogenized patients applied vaginal progesterone gel (4% or 8%) every other day for six doses per month. The Hopkins Symptom Checklist (HSCL), a psychometric profile test, was administered at baseline, day 13 of cycle 2, day 24 of cycle 2, and day 24 of cycle 3. Application of the progesterone gel caused no significant change in HSCL total scores or individual symptom scores for somatization, obsession-

compulsion, interpersonal sensitivity, depression, and anxiety. Natural vaginal progesterone gel can be an effective alternative to oral progesterone for women on HRT.

Menopause

Obstet Gynecol. August 1999; 94 (2): 225-228.

Transdermal Progesterone Cream for Vasomotor Symptoms and Postmenopausal Bone Loss.

Leonetti, H.B., M.D., Longo, S., M.D., Anasti, J.N., M.D.

Objective: To determine effectiveness of transdermal progesterone cream for controlling vasomotor symptoms and preventing postmenopausal bone loss.

Methods: We randomly assigned 102 healthy women within 5 years of menopause to transdermal progesterone cream or placebo. Study subjects and investigators were masked until data analysis was completed. An initial evaluation included complete history, physical examination, bone mineral density determination, and serum studies (TSH, FSH, lipid profile, and chemistry profile). Subjects were instructed to apply a quarter teaspoon of cream (containing 20 mg progesterone or placebo) to the skin daily. Each woman received daily multivitamins and 1200 mg of calcium and was seen every 4 months for review of symptoms. Bone scans and serum chemistries were repeated after 1 year.

Results: Thirty of the 43 (69%) in the treatment group and 26 of the 47 (55%) in the placebo group complained initially of vasomotor symptoms. Improvement or resolution of vasomotor symptoms, as determined by review of weekly symptom diaries, was noted in 25 of 30 (83%) treatment subjects and five of 26 (19%) placebo subjects ($P < .001$). However, the number of women who showed gain in bone mineral density exceeding 1.2% did not differ ($\alpha = .05$, power of 80%).

Conclusion: Although we found no protective effect on bone density after 1 year, we did see a significant improvement in vasomotor symptoms in the treated group.

J Womens Health Gend Based Med. 2000; 9 (4): 381-387.

Comparison of Regimens Containing Oral Micronized Progesterone or Medroxyprogesterone Acetate on Quality of Life in Postmenopausal Women: A Cross-Sectional Survey.

Fitzpatrick, L.A., M.D., Pace, C., BS, Wiita, B., Ph.D

A cross-sectional survey was conducted to examine quality of life (QOL) related to physiological, somatic, and vasomotor effects of changing progestogen treatment from medroxyprogesterone acetate (MPA) to micronized progesterone in postmenopausal women. Eligible women ($n = 176$) were currently using hormone replacement therapy (HRT) containing micronized progesterone for 1–6 months and had previously received HRT containing MPA. QOL was assessed via telephone interview using the Greene Climacteric Scale and the Women's Health Questionnaire. When compared with the MPA-containing regimen, women using micronized progesterone-containing HRT experienced significant improvement in vasomotor symptoms, somatic complaints, and anxiety and depressive symptoms. Women reported improved perceptions of their patterns of vaginal bleeding and control of menopausal symptoms while on the micronized progesterone-containing regimen. Approximately 80% of women reported overall satisfaction with the micronized progesterone-containing regimen. A micronized progesterone-containing HRT regimen offers the potential for improved QOL as measured by improvement of menopause-associated symptoms.

Obstet Gynecol. November 2002; 100 (5 Pt 1): 853-863.

Bleeding Patterns of the Hormone Replacement Therapies in the Postmenopausal Estrogen and Progestin Interventions Trial.

Lindenfeld, E.A., M.D., MPH, Langer, R.D., M.D., MPH.

Objective: To explore whether significant differences exist between bleeding patterns with common regimens of hormone replacement therapy using two different progestogens.

Methods: A total of 875 women in the Postmenopausal Estrogen and Progestin Interventions Trial took either placebo, conjugated equine estrogen 0.625 mg, conjugated equine estrogen 0.625 mg plus medroxyprogesterone acetate 2.5 mg in a continuous fashion, or conjugated equine estrogen 0.625 mg daily plus either cyclical medroxyprogesterone acetate 10 mg or cyclical micronized progesterone 200 mg/day for 12 days per month. Bleeding days, amounts, and episodes were recorded in diaries and aggregated by 6-month intervals for 3 years for the 596 participants with a uterus. Any bleeding for women on continuous regimens, or more than 6 episodes of bleeding per 6-month period for cyclical regimens, was considered excess.

Results: Conjugated equine estrogen plus micronized progesterone cyclical was associated with fewer excess episodes of bleeding than conjugated equine estrogen plus medroxyprogesterone acetate continuous in the first 6 months. Quantities of bleeding for conjugated equine estrogen plus micronized progesterone cyclical were less than for conjugated equine estrogen plus medroxyprogesterone acetate cyclical through 30 months and for the number of bleeding days through study end. The 3-year cumulative quantities, days, and episodes of bleeding were significantly lower for conjugated equine estrogen plus micronized progesterone cyclical than for conjugated equine estrogen plus medroxyprogesterone acetate cyclical. Placebo treated women had scant bleeding and conjugated equine estrogen had modest amounts relative to the combination therapies.

Conclusion: The bleeding measures for conjugated equine estrogen plus micronized progesterone cyclical showed consistent advantages over those for cyclical conjugated equine estrogen plus medroxyprogesterone acetate in terms of quantity, length, and episodes of bleeding. In the first 6 months, conjugated equine estrogen plus micronized progesterone cyclical had fewer excess bleeding episodes than continuous conjugated equine estrogen plus medroxyprogesterone acetate.

Pregnancy

Eur J Obstet Gynecol Reprod Biol. 2006; 129: 111–118.

Progesterone for the prevention of preterm birth: A critical evaluation of evidence

Coomarasamy, A., Thangaratinam, S., et al.

A systematic review of the literature identified nine randomized trials that evaluated the effects of progestational agents in the prevention of preterm delivery. These studies were of variable quality. Meta-analyses showed reductions in delivery rates before 37 weeks (OR 0.42, 95% CI 0.31–0.57) and 34 weeks (OR 0.51, 95% CI 0.34–0.77) as well as in respiratory distress syndrome (OR 0.55, 95% CI 0.31–0.96) with progestational agents. A cumulative meta-analysis showed that the treatment benefit for the outcome of delivery before 37 weeks exceeded the conventional level of statistical significance in 1975 ($p < 0.01$); by 1985, the p -value was < 0.001 , and by 2003, it was < 0.0001 . Another cumulative meta-analysis in which the studies were added to the pooled analysis by decreasing quality score showed significant benefit even when the analysis was limited to just the highest quality trials (OR 0.47, 95% CI 0.33, 0.66, $p < 0.0001$). An exploration of the applicability of the effects across various baseline risks using a L'abbe plot found that the benefit was consistent across a range of risks. A comprehensive review of both trial and observational data on harm did not show any demonstrable evidence of harm to mother and baby. Women at high risk of preterm birth should be recommended progestational agent therapy.

Hum Reprod. 1999; 14 (8): 1944-1948.

Luteal Support with Micronized Progesterone Following In-Vitro Fertilization using a Down-Regulation Protocol with Gonadotrophin-Releasing Hormone Against: A Comparative Study Between Vaginal and Oral Administration.

Freidler, S., Raziel, A., Schachter, M., et al.

This study aimed to compare the efficacy of micronized progesterone administered as luteal support following ovulation induction for in-vitro fertilization (IVF)-embryo transfer in cycles using gonadotropin-releasing hormone agonist, either orally (200 mgx4/day) or vaginally (100 mgx2/day) and to characterize the luteal phase hormonal profile during such treatments. A total of 64 high responder patients requiring intracytoplasmic sperm injection due to male factor infertility were prospectively randomized into two treatment groups. Patients treated orally or vaginally were comparable in age (31.9 ± 6.1 versus 30.6 ± 5.2 ; mean \pm SD), number of oocytes retrieved (17 ± 8.2 versus 18 ± 7.0), and number of embryos transferred (3.1 ± 1.2 versus 2.7 ± 0.9) per cycle. Following low dose vaginal treatment, a significantly higher implantation rate (30.7 versus 10.7%, $P < 0.01$), but similar clinical pregnancy rate (47.0 versus 33.3%) and ongoing pregnancy rate (41.1 versus 20.0%) was observed, compared with oral treatment. In conception cycles, luteal serum progesterone and oestrogen concentrations did not differ between the treatment groups. In non-conception cycles, late luteal progesterone concentrations were significantly lower following vaginal treatment. As low dose micronized progesterone administered vaginally is simple, easy and well tolerated, it could be recommended as the method of choice for luteal support, especially for high responder patients at risk for ovarian hyperstimulation syndrome.

Ann NY Acad Sci. 2004; 1034: 200-210.

Effects of Vaginal Progesterone on Pain and Uterine Contractility in Patients with Threatened Abortion before Twelve Weeks of Pregnancy.

Palagiano, A., et al.

Fifty women with previous diagnosis of inadequate luteal phase and threatened abortion underwent a prospective, randomized, double-blind study in one medical center carried out with a parallel trial. The primary objective was to establish the effects of vaginal progesterone (Crinone 8%) in reducing both pain and uterine contractions (UCs). The gel with or without (placebo) vaginal progesterone was administered once a day since the diagnosis of threatened abortion and for 5 days. The efficacy on pain symptom amelioration was evaluated by a 5-score intensity gradation, while the UCs were evaluated by ultrasound. The secondary objective of the study was to evaluate the outcome of the pregnancies. The use of progesterone was effective both on pain relief and on the frequency of the UCs that decreased after 5 days of vaginal progesterone administration ($P < 0.005$). The evaluation of the ongoing pregnancy and spontaneous abortion in both study groups after 60 days showed that 4 patients of group A and 8 patients of group B miscarried ($P < 0.05$). In conclusion, patients with threatened abortion benefit from vaginal progesterone by a reduction of UCs and pain. The use of vaginal progesterone improved the outcome of pregnancies complicated by threatened abortion and previous diagnosis of inadequate luteal phase.

Estrogens

Breast

Obstet Gynecol. 2006; 108: 1354–60.

Breast Cancer Risk in Postmenopausal Women Using Estrogen-Only Therapy

Lyytinen, H., Pukkala, E., Ylikorkala, O.

Objective: To evaluate whether the risk of estrogen only therapy on breast cancer varies by dose, constituent, and route of administration.

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. They were followed for breast cancer with the aid of the Finnish Cancer Registry to the end of 2002.

Results: Altogether, 2,171 women with breast cancer were identified. The standardized incidence ratio of breast cancer with systemic estradiol for less than 5 years was 0.93 (95% confidence interval 0.80 – 1.04), and for estradiol use for 5 years or more, 1.44 (1.29 – 1.59). Oral and transdermal estradiol was accompanied by a similar risk of breast cancer. The risk was most prominent with the dose greater than 1.9 mg/d orally; whereas the risk associated with transdermal route was not dose-dependent. The standardized incidence ratio for the lobular type of breast cancer (1.58) was slightly higher than that for the ductal type (1.36). The use of estradiol was associated with both localized breast cancer (1.45; 1.26–1.66) and cancer spread to regional nodes (1.35; 1.09–1.65). The incidence of carcinoma in situ (n_32) was increased (2.43; 1.66 – 3.42) among estradiol users.

Conclusion: Estradiol for 5 years or more, either orally or transdermally, means 2–3 extra cases of breast cancer per 1,000 women who are followed for 10 years. Oral estradiol use for less than 5 years, oral estriol, or vaginal estrogens were not associated with a risk of breast cancer.

Estradiol

Bone

J Clin Endocrinol Metab. 2000; 85: 4462-4469.

The Effect of Low Dose Micronized 17 β -Estradiol on Bone Turnover, Sex Hormone Levels, and Side Effects in Older Women: A Randomized , Double Blind, Placebo-Controlled Study.

Prestwood, K., et al.

The purpose of this study was to examine the effects of three doses (0.25, 0.5, and 1.0 mg/day) of micronized 17 β -estradiol on bone turnover, sex hormone levels, and side effects compared with placebo in healthy older women. The study design was randomized, double blind, and placebo controlled. The setting was a university clinical research center. Healthy, community-living women over 65 yr of age participated in the study. The main outcome measures were serum and urinary biochemical markers of bone resorption and formation at baseline, 6 and 12 weeks on treatment, and 6 and 12 weeks off treatment. Markers of bone resorption were N-telopeptides of type I collagen, C-telopeptides of type I collagen, and total deoxypyridinoline cross-links; formation markers were bone alkaline phosphatase, osteocalcin, and N-terminal procollagen peptides. We also measured serum estradiol, estrone, and sex hormone-binding globulin levels at baseline, 12 weeks on treatment, and 12 weeks posttreatment. All

markers of bone resorption significantly decreased at 12 weeks on treatment compared with placebo and returned toward baseline at 12 weeks posttreatment. Two markers of bone formation, bone alkaline phosphatase and N-terminal procollagen peptides, significantly decreased 12 weeks posttreatment, but the decrease in osteocalcin varied with time and estrogen dose. Based on equivalence testing, the response of markers of bone turnover to therapy with 0.25 mg/day was similar to that seen with 1.0 mg/day. Serum estradiol increased compared with baseline in all treatment groups and compared with placebo in the two higher dose groups. Breast tenderness, bleeding, and endometrial changes were significantly less frequent in the 0.25 mg/day and placebo groups compared with the higher dose groups. We conclude that low dose of estrogen (0.25 mg/day 17 β -estradiol) reduced bone turnover to a similar degree as that seen with usual replacement therapy (1.0 mg/day 17 β -estradiol), but had a side effect profile similar to that of placebo. In our study additional increases in estradiol levels, as seen with 0.5 and 1.0 mg/day 17 β -estradiol treatment, resulted in more side effects without evidence of additional benefit to bone. These data suggest that 0.25 mg/day 17 β -estradiol may be an effective and tolerable agent for the treatment of osteoporosis in older women.

Cardiovascular

Hum Reprod. 2006; 21 (10): 2715-2720.

Differential effects of oral conjugated equine estrogens and transdermal estrogen on atherosclerotic vascular disease (ASVD) risk markers and endothelial function in healthy postmenopausal women.

Yen-Ping Ho, J., et al.

Background: Recent studies have revealed that HRT may increase the risk for atherosclerotic vascular disease (ASVD).

Methods: We investigated the effects of HRT via different administration routes on the markers for ASVD and endothelial function in healthy postmenopausal women. The oral HRT group (n = 18) received conjugated equine estrogen 0.625 mg/day; the transdermal HRT group (n = 18) received 17 β -estradiol (E2) gel 0.6 mg/day for 6 months. The control group (n = 30) had no treatment for 6 months.

Results: The C-reactive protein (CRP) rose from 0.129 ± 0.116 to 0.752 ± 0.794 mg/dl ($P < 0.01$) in the oral HRT group but remained unchanged in the transdermal HRT and control groups. The flow-mediated vasodilation (FMD) in the brachial artery was increased significantly by HRT from 6.0% before oral HRT to 14.7% after oral HRT ($P < 0.001$) and from 5.9% before transdermal HRT to 13.9% after transdermal HRT ($P = 0.001$).

Conclusion: These data suggest that oral estrogen induces ASVD risk by increasing acute inflammation; however, transdermal estrogen avoids this untoward effect. Additionally, transdermal estrogen exerts a positive effect on endothelial function similar to that of oral estrogen. Therefore, the transdermal route might be favourable in terms of ASVD risks.

Estriol

Bone

Maturitas. 1997; 28 (1): 11-17.

Comparison of the Long-term Effects of Oral Estriol with the Effects of Conjugated Estrogen, 1-d-Hydroxyvitamin D3 and Calcium Lactate on Vertebral Bone Loss in Early Menopausal Women.

Itoi, H., Minakami, H., Satom, I.

We investigated the long-term effects of oral estriol (E_3) on bone mineral density (BMD) at the lumbar spine and biochemical indices of bone turnover in early menopausal women. We studied 64 healthy early menopausal women who were treated for 24 months with 2.0 mg E_3 plus 2.5 mg medroxyprogesterone acetate daily (E_3 group, $n = 15$), 0.625 mg of conjugated estrogen plus 2.5 mg medroxyprogesterone acetate daily (CE group, $n = 19$), 1.0 μ g 1- α -hydroxyvitamin D, daily (D3 group, $n = 13$), or 1.8 g calcium lactate containing 250 mg of elemental calcium daily (Ca group, $n = 17$). The BMD at the third lumbar vertebra was determined by quantitative computed tomography, and serum levels of osteocalcin (OC) and total alkaline phosphatase (Alp), as well as urinary ratios of calcium-to-creatinine (Ca/Cr) and hydroxyproline-to-creatinine (Hyp/Cr), were evaluated at baseline and every 6 months. After 24 months of treatment, the BMD decreased significantly by $12 \pm 4.5\%$ (mean \pm SE.) in the D3 group and $14 \pm 2.5\%$ in the Ca group, but not in the E_3 group ($-4.1 \pm 4.8\%$ from baseline) and in the CE group ($-0.9 \pm 3.2\%$ from baseline). The serum levels of Alp and OC decreased or remained unchanged in the E_3 and CE groups, but increased in the D3 and Ca groups. The urinary Ca/Cr was decreased in the E_3 and CE groups, but not in the D, and Ca groups. The urinary Hyp/Cr decreased in the CE group, was unchanged in the E_3 and D, groups, and increased in the Ca group. Uterine bleeding occurred less frequently in the E_3 than in the CE group (2.4 ± 4.2 versus 13.1 ± 14.8 days/person per year, $P < 0.001$). The bone-preserving effect of 2.0 mg of oral E_3 was comparable to that of 0.625 mg of conjugated estrogen and was superior to that of 1.0 μ g 1- α -hydroxyvitamin D, and 1.8 g Ca. Our findings suggest that a reduction in bone turnover in the E_3 group may have contributed to the preservation of bone.

Int J Gyn Obstet. 2006; 92: 141-142.

Estriol, conjugated equine estrogens, and alendronate therapy for osteoporosis.

Terauchi, M., et al.

This study retrospectively evaluated the efficacy of various medications prescribed to women for osteoporosis between 1992 and 2005 at the Menopause Clinic of Tokyo Medical and Dental University Hospital, Japan. Inclusion criteria were being postmenopausal; having been diagnosed with primary osteoporosis according to the criteria of the Japanese Society for Bone and Mineral Research; being aged between 40 and 69 years; and having been treated for 2 or more years with a single medication.

Multiple Sclerosis

Ann Neurol. October 2002; 52 (4): 421-428.

Treatment of Multiple Sclerosis with the Pregnancy Hormone Estriol.

Sicotte, N.L., M.D., Liva, S.M., Ph.D., et. al.

Multiple sclerosis patients who become pregnant experience a significant decrease in relapses that may be mediated by a shift in immune responses from T helper 1 to T helper 2. Animal models of multiple sclerosis have shown that the pregnancy hormone, estriol, can ameliorate disease and can cause an immune shift. We treated nonpregnant female multiple sclerosis patients with the pregnancy hormone estriol in an attempt to recapitulate the beneficial effect of pregnancy. As compared with pretreatment baseline, relapsing remitting patients treated with oral estriol (8mg/day) demonstrated significant decreases in delayed type hypersensitivity responses to tetanus, interferon- γ levels in peripheral blood mononuclear cells, and gadolinium enhancing lesion numbers and volumes on monthly cerebral magnetic resonance images. When estriol treatment was stopped, enhancing lesions increased to pretreatment levels. When estriol treatment was reinstated, enhancing lesions again were significantly decreased. Based on these results, a larger, placebo-controlled trial of estriol is warranted in women with relapsing remitting multiple sclerosis. This novel treatment strategy of using pregnancy doses of estriol in multiple sclerosis has relevance to other autoimmune diseases that also improve during pregnancy.

Vaginal

NEJM. 1993; 329 (11): 753-756.

A Controlled Trial of Intravaginal Estriol in Postmenopausal Women with Recurrent Urinary Tract Infection

Raz, P., Stamm, W.E.

Background: Recurrent urinary tract infections are a problem for many postmenopausal women. Estrogen replacement restores atrophic mucosa, lowers vaginal pH, and may prevent urinary infections.

Methods: We enrolled 93 postmenopausal women with a history of recurrent urinary tract infections in a randomized, double-blind, placebo-controlled trial of a topically applied intravaginal estriol cream. Midstream urine cultures were obtained at enrollment, monthly for eight months, and whenever urinary symptoms occurred. Vaginal cultures and pH measurements were obtained at entry and after one and eight months. The women were assigned to receive either estriol (n=50) or placebo (n=43), both administered intravaginally; 36 and 24, respectively, completed the eight months of follow-up.

Results: The incidence of urinary tract infection in the group given estriol was significantly reduced as compared with that in the group given placebo (0.5 vs. 0.9 episodes per patient-year, $P<0.001$). Survival analysis showed that more of the women in the estriol group than in the placebo group remained free of urinary tract infection ($P<0.001$). Lactobacilli were absent in all vaginal cultures before treatment and reappeared after one month in 22 of 36 estriol-treated women (61 percent) but in none of the 24 placebo recipients ($P<0.001$). With estriol the mean vaginal pH declined from 5.5 to 3.8 ($P<0.001$), whereas there was no significant change with placebo. The rate of vaginal colonization with Enterobacteriaceae fell from 67 percent to 31 percent in estriol recipients but was virtually unchanged (from 67 to 63 percent) in the placebo recipients ($P<0.005$). Side effects were minor, but caused 10 estriol recipients (28 percent) and 4 placebo recipients (17 percent) to discontinue treatment.

Conclusion: The intravaginal administration of estriol prevents recurrent urinary tract infections in postmenopausal women, probably by modifying the vaginal flora.

Maturitas. 1995; 22 (3): 227-232.

Transvaginal estriol administration in postmenopausal women: a double blind comparative study of two different doses

Bottiglionea, F., Volpeb, A., et al.

A group of 72 postmenopausal women were treated for 4 weeks with vaginal suppositories containing 0.5 or 1 mg of estriol. The two different doses achieved in identical significant improvement of urogenital symptoms, while a dose-related effect seen to be on climacteric complaints, according to a good absorption of estriol by the vaginal epithelium. Minimal side effects were observed and the safety of vaginal estriol treatment could advise further study about the effect of this kind of treatment on the climacteric syndrome.

Testosterone

General

J Clin Endocrinol Metab. 2006; 91: 136-144.

Pharmacokinetics of a Testosterone Gel in Healthy Postmenopausal Women

Singh, A., et al.

Background: The paucity of pharmacokinetic data on androgen formulations in women has hindered clinical trials of testosterone supplementation in women.

Objective: The objective of this study was to determine the time course and profile of serum testosterone concentrations during treatment with different doses of testosterone gel in postmenopausal women and assess whether estrogen treatment affects the pharmacokinetics of testosterone gel.

Methods: Postmenopausal women with total testosterone levels less than 33 ng/dl after baseline 24-h sampling were treated with 4.4, 8.8, or 13.2 mg testosterone gel daily for 7 d each in random order, with a 7-d washout period between doses. We studied 13 women who had not received estrogen therapy (group I) and 13 who had received stable estrogen therapy for 3 months or more (group II). Total and free testosterone concentrations were measured for 48 h on the seventh day of each dose administration.

Results: Twenty-six women were randomized; of these, 24 were evaluable, 13 in group I and 11 in group II. The average steady-state concentrations (Cav) of serum total and free testosterone increased with increasing testosterone dose and were highly correlated with the dose (dose effect, $P = 0.00001$), but were not affected by estrogen therapy ($P = 0.43$). In both groups, the 4.4-mg dose increased Cav total and free testosterone into the mid- to high-normal range, whereas 8.8- and 13.2-mg doses raised total (Cav: 22.3, 51.6, 80.3, and 92.0 ng/dl in group I; 22.7, 59.8, 82.0, and 114.3 ng/dl in group II at 0, 4.4, 8.8, and 13.2 mg, respectively) and free testosterone (5.9, 8.4, 11.5, 12.8 pg/ml in group I and 5.0, 7.6, 11.1, 10.8 in group II, respectively, at the various doses) above the physiological range. The area under the curve, maximum and minimum concentrations, and the change in Cav for total and free testosterone were dose related and significantly higher during administration of the 13.2-mg dose than during the 0- or 4.4-mg dose; estrogen therapy had no significant effect on these measures. Serum estradiol, LH, FSH, and SHBG levels did not change significantly at any dose. Testosterone gel was well tolerated.

Conclusion: Administration of testosterone gel to postmenopausal women raised total and free testosterone concentrations in proportion to the administered dose without affecting estradiol levels. A 4.4-mg dose raised testosterone levels into the mid- to high-normal range. Previous estrogen therapy had no significant effect on testosterone pharmacokinetics over this short duration.

Gynecol Endocrinol. 2005; 20 (5): 243-248.

Percutaneous administration of testosterone gel in postmenopausal women – a pharmacological study

Nathorst-Boos, J.

We wished to investigate if a testosterone gel administered percutaneously to postmenopausal women could result in stable serum levels of the hormone and which dose was required to produce levels within the normal premenopausal range. Fifteen postmenopausal women, mean age 55.3 years (range 45–70 years), volunteered to participate in the study and were divided into three groups. They received 10, 20 or 30 mg of testosterone as a 1% testosterone hydroalcoholic gel at 09.00 hours daily for 14 days. The gel was applied in a thin layer on the outside of the thigh each morning, over an area of approximately 15 cm². Blood samples were collected hourly between 09.00 and 17.00 hours on days 1 and 14, and also at 08.00 hours on days 3, 5, 11, 12, 13 and finally day 16, i.e. 2 days after termination of treatment. The mean basal serum level of testosterone was 1.1+0.9 nmol/l and for 5 α -dihydrotestosterone 208+143 pmol/l. There was a clear increase from the 10 mg to the 20 mg treatment (mean testosterone level during treatment 3.2 and 7.2 nmol/l, respectively) while serum testosterone values after 30 mg showed very little further increase (mean 7.5 nmol/l). Values for days 3–5 were quite similar to those for days 13–14. The present study suggests that adequate and acceptable serum levels of testosterone can be achieved with 10 mg testosterone applied transdermally.

Libido

Maturitas. 2006; 53 (1): 11-18.

Treatment with percutaneous testosterone gel in postmenopausal women with decreased libido – effects on sexuality and psychological general well-being

Nathorst-Boos, J.

Objectives: To elucidate if percutaneous treatment with 10 mg testosterone per day could enhance sexuality and psychological well-being in postmenopausal women presenting problems with low libido. Secondary to study the influence on blood lipids, hemoglobin and erythropoietin levels.

Methods: Fifty-three postmenopausal women participated. As a complement to their already on-going HRT, 10 mg of a testosterone gel (Testogel, Besins–Iscovesco) or placebo was administered. Treatment continued for three plus three months in a double blind, randomized, crossover design.

Results: The scores concerning “frequency of sexual activity, orgasm and intercourse”, “sexual arousal, fantasies and enjoyment”, “satisfaction with orgasms”, and “interest in sex” were all significantly improved for testosterone addition as compared to placebo both before and after crossover. Testosterone levels increased more than 10-fold during treatment while DHT-levels were more than doubled. Estrogen levels were not affected during the addition of testosterone. Liver enzymes, total cholesterol, triglycerides, HDL and LDL revealed no significant differences between any of the periods or groups. Endometrial thickness did not change significantly during treatment. Hemoglobin and erythropoietin remained unchanged. No significant differences in the number of experienced side effects were found.

Conclusion: Testosterone gel of 10 mg had positive effects on several aspects of sexual life such as frequency of sexual activity, orgasm, arousal, fantasies and sexual interest in postmenopausal women on HRT. Several psychological variables were positively influenced. The given dose resulted in too high serum levels. Even if no negative effects were observed, monitoring of serum levels and a decreased dose should be considered in future studies.

DHEA

Bone

J Clin Endocrinol Metab. 2006; 91: 2986–2993.

Effects of Dehydroepiandrosterone Replacement Therapy on Bone Mineral Density in Older Adults: A Randomized, Controlled Trial

Jankowski, C.M., Gozansky, W.S.

Context: Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) decrease with aging and are important androgen and estrogen precursors in older adults. Declines in DHEAS with aging may contribute to physiological changes that are sex hormone dependent.

Objective: The aim was to determine whether DHEA replacement increases bone mineral density (BMD) and fat-free mass.

Design, Setting, and Participants: A randomized, double-blinded, controlled trial was conducted at an academic research institution. Participants were 70 women and 70 men, aged 60–88 yr, with low serum DHEAS levels.

Intervention: The intervention was oral DHEA 50 mg/d or placebo for 12 months.

Measurements: BMD, fat mass, and fat-free mass were measured before and after intervention.

Results: Intent-to-treat analyses revealed trends for DHEA to increase BMD more than placebo at the total hip (1.0%, $P < 0.05$), trochanter (1.2%, $P = 0.06$), and shaft (1.2%, $P = 0.05$). In women only, DHEA increased lumbar spine BMD (2.2%, $P < 0.04$; sex-by-treatment interaction, $P < 0.05$). In secondary compliance analyses, BMD increases in hip regions were significant (1.2–1.6%; all $P < 0.02$) in the DHEA group. There were no significant effects of DHEA on fat or fat-free mass in intent-to-treat or compliance analyses.

Conclusions: DHEA replacement therapy for 1 yr improved hip BMD in older adults and spine BMD in older women. Because there have been few randomized, controlled trials of the effects of DHEA therapy, these findings support the need for further investigations of the benefits and risks of DHEA replacement and the mechanisms for its actions.

General

Alt Med Review. 1996; 1 (2): 60-69.

Dehydroepiandrosterone: Biological Effects and Clinical Significance

Gaby, A., M.D.

Dehydroepiandrosterone (DHEA) is a steroid hormone secreted in greater quantity by the adrenal glands than any other adrenal steroid. For many years, scientists assumed that DHEA merely functioned as a reservoir upon which the body could draw to produce other hormones, such as estrogen and testosterone. However, the recent identification of DHEA receptors in the liver, kidney and testes of rats strongly suggests that DHEA may have specific physiologic actions of its own. Circulating levels of DHEA decline progressively with age; this age-related decline does not occur with any of the other adrenal steroids. Epidemiologic evidence indicates that higher DHEA levels are associated with increased longevity and prevention of heart disease and cancer, suggesting that some of the manifestations of aging may be caused by DHEA deficiency. Animal and laboratory data indicate that administration of DHEA may prevent obesity, diabetes, cancer (breast, colon and liver), and heart disease; enhance the functioning of the immune system; and prolong life. In humans, evidence exists that DHEA might be associated with autoimmune diseases such as lupus, rheumatoid arthritis and multiple sclerosis; chronic fatigue syndrome; acquired immunodeficiency syndrome (AIDS); allergic

disorders; osteoporosis; and Alzheimer's disease. Although administration of DHEA appears to be safe, its long-term effects are unknown, and it is possible that adverse consequences will become evident with chronic use. It is therefore important that this hormone be used with care and that practitioners err on the side of caution when contemplating DHEA supplementation.

General

Arch Gen Psychiatry. 2005; 62: 154-162.

Dehydroepiandrosterone Monotherapy in Midlife-Onset Major and Minor Depression

Schmidt, P., Daly, R.

Context: Alternative and over-the-counter medicines have become increasingly popular choices for many patients who prefer not to take traditional antidepressants. The adrenal androgen and neurosteroid dehydroepiandrosterone (DHEA) is available as over-the counter hormonal therapy and previously has been reported to have antidepressant-like effects.

Objective: To evaluate the efficacy of DHEA as a monotherapy treatment for midlife-onset depression.

Design: A double-blind, randomized, placebo controlled, crossover treatment study was performed from January 4, 1996, through August 31, 2002.

Settings: The National Institute of Mental Health Midlife Outpatient Clinic in the National Institutes of Health Clinical Center, Bethesda, Md.

Patients: Men (n=23) and women (n=23) aged 45 to 65 years with midlife-onset major or minor depression participated in this study. None of the subjects received concurrent antidepressant medications.

Intervention: Six weeks of DHEA therapy, 90 mg/d for 3 weeks and 450 mg/d for 3 weeks, and 6 weeks of placebo.

Main Outcome Measures: The 17-Item Hamilton Depression Rating Scale and Center for Epidemiologic Studies Depression Scale. Additional measures included the Derogatis Interview for Sexual Functioning. Results were analyzed by means of repeated-measures analysis of variance and post hoc Bonferroni t tests.

Results: Six weeks of DHEA administration was associated with a significant improvement in the 17-Item Hamilton Depression Rating Scale and the Center for Epidemiologic Studies Depression Scale ratings compared with both baseline (P_.01) and 6 weeks of placebo treatment (P_.01). A 50% or greater reduction in baseline Hamilton Depression Rating Scale scores was observed in 23 subjects after DHEA and in 13 subjects after placebo treatments. Six weeks of DHEA treatment also was associated with significant improvements in Derogatis Interview for Sexual Functioning scores relative to baseline and placebo conditions.

Conclusion: We find DHEA to be an effective treatment for midlife-onset major and minor depression.

Diabetes. 2005; 54: 765-769.

Effect of Dehydroepiandrosterone Replacement on Insulin Sensitivity and Lipids in Hypoadrenal Women

Dhatariya, K., Bigelow, M.L., Sreekumaran, N.K.

DHEA (dehydroepiandrosterone) replacement is not part of the current standard of care in hypoadrenal subjects. Animal studies have shown that DHEA administration prevents diabetes. To determine the physiological effect of DHEA replacement on insulin sensitivity in adrenal-deficient women, we performed a single-center, randomized, double-blind, placebo-controlled, crossover study in 28 hypoadrenal women (mean age 50.2 ± 2.87 years) who received a single 50-mg dose of DHEA daily or placebo. After 12 weeks, insulin sensitivity was assessed using a hyperinsulinemic-euglycemic clamp. DHEA replacement significantly increased DHEA-S (sulfated ester of DHEA), bioavailable testosterone, and androstenedione and reduced sex hormone binding globulin levels. Fasting plasma

insulin and glucagon were lower with DHEA (42 ± 4.94 vs. 53 ± 6.58 pmol/l [$P = 0.005$] and 178 ± 11.32 vs. 195.04 ± 15 pmol/l [$P = 0.02$], respectively). The average amount of glucose needed to maintain similar blood glucose levels while infusing the same insulin dosages was higher during DHEA administration (358 ± 24.7 vs. 320 ± 24.6 mg/min; $P < 0.05$), whereas endogenous glucose production was similar. DHEA also reduced total cholesterol ($P < 0.005$), triglycerides ($P < 0.011$), LDL cholesterol ($P < 0.05$), and HDL cholesterol ($P < 0.005$). In conclusion, replacement therapy with 50 mg of DHEA for 12 weeks significantly increased insulin sensitivity in hypoadrenal women, thereby suggesting that DHEA replacement could have a potential impact in preventing type 2 diabetes.

Combination Hormones

Breast

American Society for Reproductive Medicine. April 1995; 63 (4): 785-791.

Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo.

Chang, K.J., M.D., Lee, T.Y., M.D., et. al.

Objective To study the effect of E2 and P on the epithelial cell cycle of normal human breast in vivo.

Design Double-blind, randomized study. Topical application to the breast of a gel containing either a placebo, E2, P, or a combination of E2 and P, daily, during the 10 to 13 days preceding breast surgery.

Patients Forty premenopausal women undergoing breast surgery for the removal of a lump.

Main outcome measures Plasma and breast tissue concentrations of E2 and P. Epithelial cell cycle evaluated in normal breast tissue areas by counting mitoses and proliferating cell nuclear antigen immunostaining quantitative analyses.

Results Increased E2 concentration increases the number of cycling epithelial cells. Increased P concentration significantly decreases the number of cycling epithelial cells.

Conclusion Exposure to P for 10 to 13 days reduces E2-induced proliferation of normal breast epithelial cells in vivo.

Bone

Maturitas. 1995; 21(3): 227-236.

Testosterone Enhances Estradiol's Effects on Postmenopausal Bone Density and Sexuality.

Davis, S.R., McCloud, P., et. al.

To investigate the role of androgens in increasing bone density and improving low libido in postmenopausal women, we have studied the long-term effects of estradiol and testosterone implants on bone mineral density and sexuality in a prospective, 2 year, single-blind randomized trial. Thirty-four postmenopausal volunteers were randomized to treatment with either estradiol implants 5.0 mg alone (E) or estradiol 5.0 mg plus testosterone 5.0 mg (E&T), administered 3-monthly for 2 years. Cyclical oral progestins were taken by those women with an intact uterus. Thirty-two women completed the study. BMD (DEXA) of total body, lumbar vertebrae (L1-L4) and hip area increased significantly in both treatment groups. BMD increased more rapidly in the testosterone treated group at all sites. A substantially greater increase in BMD occurred in the E&T group for total body ($P < 0.008$), vertebral L1-L4 ($P < 0.001$) and trochanteric ($P < 0.005$) measurements. All sexual parameters (Sabbatsberg sexual self-rating scale) improved significantly in both groups. Addition of testosterone resulted in a significantly greater improvement compared to E for sexual activity ($P < 0.03$), satisfaction ($P < 0.03$), pleasure ($P < 0.01$), orgasm ($P < 0.035$) and relevancy ($P < 0.05$). Total cholesterol and LDL-cholesterol

fell in both groups as did total body fat. Total body fat-free mass (DEXA, anthropometry, impedance) increased in the E&T group only. We concluded that in postmenopausal women, treatment with combined estradiol and testosterone implants was more effective in increasing bone mineral density in the hip and lumbar spine than estradiol implants alone. Significantly greater improvement in sexuality was observed with combined therapy, verifying the therapeutic value of testosterone implants for diminished libido in postmenopausal women. The favourable estrogenic effects on lipids were preserved in women treated with T, in association with beneficial changes in body composition.

Cardiovascular

JAMA. 1995; 273: 199-208.

Effects of Estrogen or Estrogen/Progestin Regimens on Heart Disease Risk Factors in Postmenopausal Women: The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial

The Writing Group for the PEPI trial.

Objective: To assess pairwise differences between placebo, unopposed estrogen, and each of three estrogen/progestin regimens on selected heart disease risk factors in healthy postmenopausal women.

Design: A 3-year, multicenter, randomized, double-blind, placebo-controlled trial.

Participants: A total of 875 healthy postmenopausal women aged 45 to 64 years who had no known contraindication to hormone therapy.

Intervention: Participants were randomly assigned in equal numbers to the following groups: (1) placebo; (2) conjugated equine estrogen (CEE), 0.625 mg/d; (3) CEE, 0.625 mg/d plus cyclic medroxyprogesterone acetate (MPA), 10 mg/d for 12 d/mo; (4) CEE, 0.625 mg/d plus consecutive MPA, 2.5 mg/d; or (5) CEE, 0.625 mg/d plus cyclic micronized progesterone (MP), 200 mg/d for 12 d/mo.

Primary Endpoints. Four endpoints were chosen to represent four biological systems related to the risk of cardiovascular disease: (1) high-density lipoprotein cholesterol (HDL-C), (2) systolic blood pressure, (3) serum insulin, and (4) fibrinogen.

Analysis: Analyses presented are by intention to treat. P values for primary endpoints are adjusted for multiple comparisons; 95% confidence intervals around estimated effects were calculated without this adjustment.

Results: Mean changes in HDL-C segregated treatment regimens into three statistically distinct groups: (1) placebo (decrease of 0.03 mmol/L (1.2 mg/dL)); (2) MPA regimens (increases of 0.03 to 0.04 mmol/L (1.2 to 1.6 mg/dL)); and (3) CEE with cyclic MP (increase of 0.11 mmol/L (4.1 mg/dL)) and CEE alone (increase of 0.14 mmol/L (5.6 mg/dL)). Active treatments decreased mean low-density lipoprotein cholesterol (0.37 to 0.46 mmol/L (14.5 to 17.7 mg/dL)) and increased mean triglyceride (0.13 to 0.15 mmol/L (11.4 to 13.7 mg/dL)) compared with placebo. Placebo was associated with a significantly greater increase in mean fibrinogen than any active treatment (0.10 g/L compared with -0.02 to 0.06 g/L); differences among active treatments were not significant. Systolic blood pressure increased and postchallenge insulin levels decreased during the trial, but neither varied significantly by treatment assignment. Compared with other active treatments, unopposed estrogen was associated with a significantly increased risk of adenomatous or atypical hyperplasia (34% vs. 1%) and of hysterectomy (6% vs. 1%). No other adverse effect differed by treatment assignment or hysterectomy status.

Conclusions: Estrogen alone or in combination with a progestin improves lipoproteins and lowers fibrinogen levels without detectable effects on postchallenge insulin or blood pressure. Unopposed estrogen is the optimal regimen for elevation of HDL-C, but the high rate of endometrial hyperplasia restricts use to women without a uterus. In women with a uterus, CEE with cyclic MP has the most favorable effect on HDL-C and no excess risk of endometrial hyperplasia.

Circulation. 2007; 115: 840-845.

Hormone Therapy and Venous Thromboembolism Among Postmenopausal Women. Impact of the Route of Estrogen Administration and Progestogens: The ESTHER Study

Canonico, M., et al.

Background: Oral estrogen therapy increases the risk of venous thromboembolism (VTE) in postmenopausal women. Transdermal estrogen may be safer. However, currently available data have limited the ability to investigate the wide variety of types of progestogen.

Methods and Results: We performed a multicenter case-control study of VTE among postmenopausal women 45 to 70 years of age between 1999 and 2005 in France. We recruited 271 consecutive cases with a first documented episode of idiopathic VTE (208 hospital cases, 63 outpatient cases) and 610 controls (426 hospital controls, 184 community controls) matched for center, age, and admission date. After adjustment for potential confounding factors, odds ratios (ORs) for VTE in current users of oral and transdermal estrogen compared with nonusers were 4.2 (95% CI, 1.5 to 11.6) and 0.9 (95% CI, 0.4 to 2.1), respectively. There was no significant association of VTE with micronized progesterone and pregnane derivatives (OR, 0.7; 95% CI, 0.3 to 1.9 and OR, 0.9; 95% CI, 0.4 to 2.3, respectively). In contrast, norpregnane derivatives were associated with a 4-fold-increased VTE risk (OR, 3.9; 95% CI, 1.5 to 10.0).

Conclusions: Oral but not transdermal estrogen is associated with an increased VTE risk. In addition, our data suggest that norpregnane derivatives may be thrombogenic, whereas micronized progesterone and pregnane derivatives appear safe with respect to thrombotic risk. If confirmed, these findings could benefit women in the management of their menopausal symptoms with respect to the VTE risk associated with oral estrogen and use of progestogens.

Fertil Steril. 2001; 75 (5): 898 –915.

Effects of postmenopausal hormone replacement therapy on lipid, lipoprotein, and apolipoprotein (a) concentrations: analysis of studies published from 1974–2000

Godsland, I.F., Ph.D.

Objective: To establish reference estimates of the effects of different hormone replacement therapy (HRT) regimens on lipid and lipoprotein levels.

Design: Review and pooled analysis of prospective studies published up until the year 2000.

Setting: Clinical trials centers, hospitals, menopause clinics.

Patient(s): Healthy postmenopausal women.

Intervention(s): Estrogen alone, estrogen plus progestogen, tibolone, or raloxifene in the treatment of menopausal symptoms.

Main Outcome Measure(s): Serum high- and low-density lipoprotein (HDL and LDL) cholesterol, total cholesterol, triglycerides, and lipoprotein (a).

Result(s): Two-hundred forty-eight studies provided information on the effects of 42 different HRT regimens. All estrogen alone regimens raised HDL cholesterol and lowered LDL and total cholesterol. Oral estrogens raised triglycerides. Transdermal estradiol 17-beta lowered triglycerides. Progestogens had little effect on estrogen-induced reductions in LDL and total cholesterol. Estrogen-induced increases in HDL and triglycerides were opposed according to type of progestogen, in the order from least to greatest effect: dydrogesterone and medrogestone, progesterone, cyproterone acetate, medroxyprogesterone acetate, transdermal norethindrone acetate, norgestrel, and oral norethindrone acetate. Tibolone decreased HDL cholesterol and triglyceride levels. Raloxifene reduced LDL cholesterol levels. In 41 studies of 20 different formulations, HRT generally lowered lipoprotein (a).

Conclusion(s): Route of estrogen administration and type of progestogen determined differential effects of HRT on lipid and lipoprotein levels. Future work will focus on the interpretation of the clinical significance of these changes.

Menopause

Ann NY Acad Sci. 2005; 1057: 506-524.

Bio-identical Steroid Hormone Replacement. Selected Observations from 23 years of Clinical and Laboratory Practice.

Wright, J.

To maximize the safety and efficacy of human hormone replacement therapy, it is suggested that exact molecular copies of human hormones ("bio-identical" hormones) be administered in physiologic quantities and proportions, following physiologic timing and routes of administration. It is also suggested that physicians return to the practice of monitoring hormone therapy by precise laboratory measurement levels of the hormones administered. This paper also presents clinical and laboratory data concerning appropriate proportions of bio-identical estrogens, the physiologic and supraphysiologic nature of commonly employed doses, estrogen levels achieved by varying routes of administration, and the significant effects of iodine on estrogen metabolism and cobalt on estrogen excretion.

Climacteric. June 2003; 6: 104-111.

Pharmacokinetics of estradiol, progesterone, testosterone and dehydroepiandrosterone after transbuccal administration to postmenopausal women.

Wren, B.G., M.D., Day, R.O., McLachlan, A.J., Williams, K.M.

Objective: To evaluate the pharmacokinetic profiles of estradiol, progesterone, testosterone, and dehydroepiandrosterone in postmenopausal women following single and multiple dosing using a troche and the transbuccal route of administration.

Methods: Each troche contained estradiol (0.5 mg), progesterone (200 mg), testosterone (2 mg) and dehydroepiandrosterone (10 mg). a half troche was administered to each of six women and the plasma concentration-time profiles determined over 24 h. thereafter, a one-half troche was taken twice daily for 2 weeks and concentrations determined over a dosage interval (12 h). Blood and saliva samples were collected at specified time intervals on the first day and again after 2 weeks.

Results: Each of the hormones was readily absorbed via the buccal mucous membrane. Peak plasma concentrations of estradiol and progesterone were comparable to those found normally in young menstruating women.

Conclusion: The transbuccal route is a novel approach to provide therapy for the management of menopause-related symptoms of postmenopausal women without the need to resort to conjugated or synthesized hormones, and may overcome the poor or erratic systematic availability associated with other routes of administration.

Obstet Gynecol. 1989; 73 (4): 606-612.

Menopausal Hormone Replacement Therapy With Continuous Daily Oral Micronized Estradiol and Progesterone

Hargrove, J.T., Maxson, W.S., et al.

The safety and efficacy of a daily combination of micronized estradiol (E2) (0.7-1.05 mg) and progesterone (200-300 mg) were evaluated in ten menopausal women with moderate to severe vasomotor symptoms and/or vaginal atrophy over a 12-month study interval. For comparison, five

similar women were placed on conjugated estrogens, 0.625 mg daily, and medroxyprogesterone acetate, 10 mg daily, for the first 10 days of each calendar month for 12 months. Patients were evaluated at 0, 1, 3, 6, and 12 months. Estrogens rose significantly from baseline in both groups ($P < .01$). Progesterone increased significantly above baseline in the E2 and progesterone group ($P < .01$), but did not change in the conjugated estrogens and medroxyprogesterone acetate users. All women on E2 and progesterone had a decrease in total cholesterol and an increase in high-density lipoprotein cholesterol from baseline ($P < .01$). Those on conjugated estrogens and medroxyprogesterone acetate had no significant change from baseline in total cholesterol; however, they did have an increase in high-density lipoprotein cholesterol values ($P < .01$). In the E2 and progesterone group, the endometrial histology became completely quiescent and there was no uterine bleeding after 6 months of observation. Four of five women on conjugated estrogens and medroxyprogesterone acetate continued regular withdrawal bleeding throughout the study period, but no endometrial hyperplasia was encountered. This study demonstrates that the daily administration of a combination of micronized E2 and progesterone results in symptomatic improvement, minimal side effects, an improved lipid profile, and amenorrhea without endometrial proliferation or hyperplasia in menopausal women.

Infertility and Reproductive Medicine Clinics of North America. 1995; 6 (4): 653-674.

An Alternative Method of Hormone Replacement Therapy Using The Natural Sex Steroids

Hargrove, J.T., Osteen, K.G.

This manuscript presents a protocol for hormone replacement therapy in postmenopausal patients with measured deficiencies of E2, testosterone, and DHEA. Formulating the appropriate replacement hormones requires individualizing therapy according to each woman's needs. Because progesterone is universally deficient in postmenopausal women, it is uniformly replaced unless precluded by side effects. Replacement dosage is accomplished by titrating the deficient steroid to levels present in premenopausal women. An appreciation of the mechanism of hormone action, the absorption kinetics of these hormones, and the first-pass effect on metabolism helps in trouble shooting problems encountered with therapy. To make valid comparisons over time, the serum hormones must be measured at a standardized time relative to the last dose. We believe this method of hormone replacement therapy is based on sound physiologic principles and represents an objective method of ensuring the establishment of premenopausal levels of circulating sex steroids. In short, it treats the menopause like a true deficiency state by correcting the measured hormone deficiencies.

Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2006; 13: 291-307.

Verified Hormone Therapy Improves Episodic Memory Performance in Healthy Postmenopausal Women.

Yonker, J., et al.

Studies of hormone therapy (HT) and cognition have yielded conflicting results. The aim of this observational study was to examine the effect of estradiol, via serum verified HT (estradiol, estriol, progesterone) and endogenous estradiol, on 108 healthy postmenopausal women's cognitive performance. The results demonstrated that the 43 HT-users performed at a significantly higher level than non-users on episodic memory tasks and on a verbal fluency task, whereas HT-users and non-users did not differ on tasks assessing semantic memory and spatial visualization. In addition, there was a positive relationship between serum estradiol level and enhanced episodic memory performance, indicating that postmenopausal HT is associated with enhanced episodic memory and verbal fluency task, independent of age and education. These observational results suggest cognitive tasks. Hormone therapy compliance and formulation is discussed as confounding factors in previous research.



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