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## **Bioidentical Hormone Replacement Therapy (BHRT) Position Paper**

As a primary care physician who specializes in natural medicine, I think the most important role doctors can play is that of teacher – to provide complete, unbiased information so that patients can make their own informed decisions. Following is a list of facts I provide my patients when they seek help for hormone-related symptoms:

- Many women and men have significant symptoms as they age.
- No two people are identical in terms of their hormone production or the symptoms they experience.
- Eating a healthy diet, exercising regularly, minimizing stress, and avoiding environmental toxins are the foundations for preventing and managing hormone-related symptoms.
- If symptoms persist, hormone replacement is an option that contains benefits and risks.
- People have different medication needs and drug detoxifying capacities. Testing baseline hormone levels and following up with repeat testing after treatment is a reasonable way to determine whether a patient is receiving too much hormone. Symptom improvement usually determines if a patient is receiving enough medication.
- Synthetic hormones (especially Provera) have been shown to have serious health consequences including increased risk of breast cancer, blood clots, heart disease, and stroke. Synthetic oral testosterone has been shown to increase the risk for liver inflammation and liver cancer.
- Bioidentical hormones are identical in structure to those made by the body. There is a large body of research involving the effectiveness of bioidentical estradiol, progesterone, and testosterone [please see references]. Bioidentical hormones do carry risks, especially when administered in excessive dosages, outside of physiological levels; overall, however, they have a lower risk profile than their synthetic counterparts (this is especially true for bioidentical progesterone vs. progestins, and bioidentical testosterone vs. methyltestosterone). More research about long-term effects of bioidentical hormones needs to be done.
- Bioidentical hormones are found in pharmaceuticals (e.g., bioidentical estradiol patches such as Climara or Vivelle, bioidentical progesterone such as Prometrium, and bioidentical testosterone such as Androderm, Androgel, or Testopel) as well as in individual preparations made by compounding pharmacists.
- Compounded medications have been available since the 1930s. Organizations such as the Professional Compounding Centers of America (PCCA) provide continuing education seminars for pharmacists and physicians, as well as a source of FDA-approved ingredients subjected to quality assurance standards.
- Treating hormone imbalances requires a comprehensive understanding of endocrinology and gynecology, as well as significant clinical experience.

I also share the following opinions with my patients:

- It makes sense to test baseline hormone production, and then if low levels and/or hormone-related symptoms deem necessary, to prescribe low dosages of bioidentical hormones that eliminate or minimize symptoms, or to bring a patient's hormone levels to within physiological range. There is no established protocol for such treatment and potential risks exist; therefore, a conservative approach to treatment is most prudent.
- Choosing an experienced physician who listens, provides you with information, and respects your treatment decisions is your right and responsibility. Expect your physician to provide you with available research, benefits, and risks of any treatment you choose. Do not be afraid to question any treatment or to make your own healthcare decisions.

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**References from personal pubmed search, Women In Balance ([www.womeninbalance.org](http://www.womeninbalance.org)), Rebecca Glaser, MD ([www.hormonebalance.org](http://www.hormonebalance.org)), & David Zava, PhD ([www.zrtlab.com](http://www.zrtlab.com))**

### **Bioidentical Estrogens & Progesterone – general**

- Holtorf K. The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer and more efficacious than commonly used synthetic versions in hormone replacement therapy? *Postgraduate Medicine* 2009;121(1):73-85.

*This paper reviews the evidence comparing bioidentical estradiol, estriol, and progesterone with commonly used synthetic HRT in terms of efficacy, physiological action on breast tissue, and risk for breast cancer and cardiovascular disease. Results were that patients reported greater satisfaction with BHRT, especially progesterone over progestins. In addition, BHRT was associated with lower breast cancer and cardiovascular disease risk.*

- L'Hermite M, Simoncini T, Fuller S, et al. Could transdermal estradiol + progesterone be a safer postmenopausal HRT? A review. *Maturitas* 2008;60(3):185-201.

*This paper reviews the role of the non-oral route of administration of bioidentical estradiol in for management of menopausal symptoms. Non-orally administered estrogens, minimizing the hepatic induction of clotting factors and others proteins associated with the first-pass effect, are associated with potential advantages on the cardiovascular system. In particular, the risk of developing deep vein thrombosis or pulmonary thromboembolism is negligible in comparison to that associated with oral estrogens. In addition, recent indications suggest potential advantages for blood pressure control with non-oral estrogens. To the same extent, a growing literature suggests that the progestins used in association with estrogens may not be equivalent. Recent evidence indeed shows that natural progesterone displays a favorable action on the vessels and on the brain, while this might not be true for some synthetic progestins. Compelling indications also exist that differences might also be present for the risk of developing breast cancer, with recent trials indicating that the association of natural progesterone with estrogens confers less or even no risk of breast cancer as opposed to the use of other synthetic progestins. In conclusion, while all types of hormone replacement therapies are safe and effective and confer significant benefits in the long-term when initiated in young postmenopausal women, in specific clinical settings the choice of the transdermal route of administration of estrogens and the use of natural progesterone might offer significant benefits and added safety.*

### **Bioidentical Estrogens:**

- Archer DF; EstroGel Study Group. Percutaneous 17beta-estradiol gel for the treatment of vasomotor symptoms in postmenopausal women. *Menopause* 2003 Nov-Dec;10(6):516-21.
- Arrenbrecht S, Boermans AJ. Effects of transdermal estradiol delivered by a matrix patch on bone density in hysterectomized, postmenopausal women: a 2-year placebo-controlled trial. *Osteoporosis Int* 2002;13(2):176-83.
- Brincat MP, Baron M, Galea R. Estrogens and the skin. *Climacteric* 2005;8:110-123.

*This paper presented conclusions from a meta-analysis of the available research regarding estrogen and skin changes in menopausal women. Estradiol supplementation, including estradiol pellet implants, have been shown to increase collagen content, dermal thickness and elasticity, as well as skin water content. In addition, studies on estrogen and wound healing suggest that estradiol supplementation may play a beneficial role in cutaneous injury repair.*

- Bruce-Keller AJ, Keeling JL, Keller JN, Huang FF, Camondola S, Mattson MP. Anti-inflammatory effects of estrogen on microglial activation. *Endocrinology* 2000 Oct;141(10):3646-56.

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*This study identified new pathways for the estrogenic anti-inflammatory effects on brain function, potentially leading to identification of new methods for improving neurodegenerative disease, specifically involving the microglial cells.*

- Callantine MR, Martin PL, Bolding OT, Warner PO, Greaney MO Jr. Micronized 17 beta-estradiol for oral estrogen therapy in menopausal women. *Obstet Gynecol* 1975 Jul;46(1):37-41.
- Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women – impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation* 2007; 115:840-845.

*This study showed that oral but not transdermal (patch) estrogens increase the risk of blood clots. In addition, it suggested that synthetic progestins increase the risk of clots, whereas micronized, bioidentical progesterone does not.*

- Chan HY, Yao X, Tsang SY, Chan FL, Lau CW, Huang Y. Different role of endothelium/nitric oxide in 17beta-estradiol- and progesterone-induced relaxation in rat arteries. *Life Sci* 2001 Aug 24;69(14):1609-17.
- Chetkowski RJ, Meldrum DR, Steingold KA, Randle D, Lu JK, Eggena P, Hershman JM, Alkjaersig NK, Fletcher AP, Judd HL. Biologic effects of transdermal estradiol. *N Engl J Med* 1986 Jun 19;314(25):1615-20.

*Twenty-three postmenopausal women were randomly assigned to use of transdermal estradiol in four increasing doses (25, 50, 75, 100 micrograms per 24 hours) followed by daily oral dose of conjugated equine estrogens in two doses (0.625 mg, 1.25 mg) or to use oral conjugated equine estrogens followed by transdermal estradiol. Results showed a dose-response relation between the amount of estradiol delivered and the serum measure of the hormone. Estrone concentrations also rose with transdermal application. At the 50 and 100 microgram transdermal dose levels, results were comparative to the 0.625 and 1.25 mg conjugated equine estrogen results. Nonhepatic markers (serum gonadotropin, vaginal cytologic studies, urinary calcium levels and urinary calcium/creatinine ratios all increased in dose-dependent fashion. Hepatic markers (hepatic protein level, lipid metabolism, clotting factors, renin substrate) were not affected by transdermal doses of estradiol. Transdermal estradiol provided benefit of increased serum hormone levels without hepatic protein effects of oral conjugated equine estrogens.*

- Collette J, Viethel P, Dethor M, Chevallier T, Micheletti MC, Foidart JM, Reginster JY. Comparison of changes in biochemical markers of bone turnover after 6 months of hormone replacement therapy with either transdermal 17 beta-estradiol or conjugated equine estrogen plus noregestrol acetate. *Gynecol Obstet Fertil.* 2003 May;31(5):434-41.
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*Twenty-two peri- or post-menopausal women with median age of 50 years experiencing moderate severity depression (DSM-IV major depression, minor depression, or dysthymia) were enrolled in a 4 week open-label clinical trial of 100 micrograms of transdermal 17B estradiol. Results showed decreased score on Montgomery-Asberg Depression Rating Scale (20 to 11.50) and Beck Depression Inventory. Greene-Climacteric Scale scores showed measured improvement during the 4 week study. Changes in depression scales and climacteric scales were not significantly correlated. Perimenopausal (6) women showed greater improvement in depression scales than postmenopausal women (2). Authors suggested this study supports previous results showing that the effect of estrogen therapy on mood may be independent of antidepressant effects mediated by alleviation of vasomotor symptoms and that*

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*estrogen therapy may be of benefit to perimenopausal women experiencing moderately severe depression.*

- Crews JK, Khalil RA. Antagonistic effects of 17 beta-estradiol, progesterone, and testosterone on Ca<sup>2+</sup> entry mechanisms of coronary vasoconstriction. *Arterioscler Thromb Vasc Biol* 1999 Apr;19(4):1034-40.
- Darj E, Axelsson O, Carlstrom K, Nilsson S, von Schoultz B. Liver metabolism during treatment with estradiol and natural progesterone. *Gynecol Endocrinol* 1993 Jun;7(2):111-4.
- Davis SR, Walker KZ, Strauss BJ. Effects of estradiol with and without testosterone on body composition and relationships with lipids in postmenopausal women. *Menopause* 2000 Nov-Dec;7(6):395-401.
- de Kleijn MJ, van der Schouw YT, Verbeek AL, Peeters PH, Banga JD, van der Graaf Y. Endogenous estrogen exposure and cardiovascular mortality risk in postmenopausal women. *Am J Epidemiol* 2002 Feb 15;155(4):339-45.
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*The authors evaluated the effects of 17 beta-estradiol in a random double-blind, dose ranging study of 41 postmenopausal women conducted in 2 phases. Phase one included phased E2 doses (0.5mg, 1.0mg, 2.0mg) plus calcium supplementation (to serum value of 1500mg). Phase two included E2 doses plus random cessation of calcium supplementation. Progestins were added during phase two (total study time of 18 months). Results showed very little change in bone density results for placebo group (0.5 - 0.9%) whereas treatment group showed significant increases from baseline bone density. In phase two the treatment groups showed an annual change in bone density of 2.0. There was a positive correlation between total calcium intake and the change in bone density results. The study showed a continuous dose-response effect on bone density results. Authors concluded that low dose (1.0mg) beta-estradiol and 1000mg of calcium prevented bone loss in postmenopausal women.*

- Evans SF, Davie MW. Low and conventional dose transdermal oestradiol are equally effective at preventing bone loss in spine and femur at all post-menopausal ages. *Clin Endocrinol (Oxf)* 1996 Jan;44(1):79-84.
- Friel PN, Hinchcliffe C, Wright JV. Hormone replacement with estradiol: conventional oral doses result in excessive exposure to estrone. *Altern Med Rev*. 2005 Mar;10(1):36-41.
- Granberg S, Eurenus K, Lindgren R, Wilhelmsson L. The effects of oral estriol on the endometrium in postmenopausal women. *Maturitas* 2002 Jun 25;42(2):149-56.

*This study conducted endometrial evaluation using both transvaginal ultrasound and histologic biopsy by Pipelle in postmenopausal women taking a low-dose oral estriol (1 or 2 mg daily) for a mean duration of 4.3 years. Mean endothelial thickness in the study group after one year was 3.0mm and in the control group was 2.4mm. There was a noted increase in atrophic vaginal epithelium in the control group. There was a noted increased incidence of endometrial polyps in the study group (14.1%) compared to the control group (2.9%) although this was not determined to be clinically significant.*

- Haines, C, Chung, T, Chang, A, Masarei, J, Tomlinson, B, Wong, E. Effect of oral estradiol on Lp(a) and other lipoproteins in postmenopausal women. A randomized, double-blind, placebo-controlled, crossover study. *Arch Intern Med* 1996 Apr 22;156(8):866-72.

*In a randomized, double-blind, placebo-controlled, crossover study, 91 surgically postmenopausal women received either 6 months of 2mg daily oral estradiol followed by 6 months of placebo or the*

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*opposite regimen. During treatment phase, Group One showed decreased Lp(a) lipoprotein concentration (10.78 to 6.44 mg/dL) and LDL-C with increase in HDL-C and TG while Group Two showed a less pronounced decrease (12.74 to 10.75). 53 women continued oral estrogen therapy for an additional 12 months. Lp(a) levels were essentially unchanged from previous measures at the end of the treatment phase after 12 months of additional therapy. Authors suggested that reduced Lp(a) lipoprotein levels with extended oral estrogen therapy support a cardioprotective effect of HRT in postmenopausal women.*

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- Haspels AA, Luisi M, Kicovic PM. Endocrinological and clinical investigations in post-menopausal women following administration of vaginal cream containing oestriol. *Maturitas* 1981 Dec;3(3-4):321-7.
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*This study contained 80 postmenopausal women, 48 of whom (60%) agreed to undergo long-term treatment with estriol suppositories. All had symptoms of vaginal atrophy and urinary incontinence. Endometrial samples were taken after 8-10 years of therapy. Estriol had induced slight proliferative changes in the endometrium in 7 of 48 patients studied by endometrial sampling. 75% of the women reported significant subjective improvement of stress incontinence. The authors conclusion was that the risk of estriol treatment is insignificant.*

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*This was a randomized comparison study (N=67) with three arms: 2.0mg estriol (E3) + 2.5mg medroxyprogesterone, 0.625mg conjugated estrogen (CE) + 2.5mg medroxyprogesterone, and a vitamin D and calcium combination (control); The study looked at changes in serum lipid profiles in early menopausal women. After 48 months on the randomized protocol, the serum lipid profiles showed that those in the E3 group decreased total cholesterol and triglycerides (-4.9 and - 6.7) compared to the control of (+5.4 and +6.1) and CE group of (-1.9 and +17.6). The E3 group showed less significant changes in HDL cholesterol and LDL cholesterol when compared to the CE protocol: E3 (+3.8 and -5.2), CE (+10.7 and -11.4), control (-3.6 and +11.8). The results show the improvement of serum lipid profiles in response to estrogen. The authors suggested that in women where bleeding has been a problem with certain estrogen protocols, low-dose estriol may be an alternative treatment for those at risk of cardiovascular disease.*

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*Doses of 100 mg of micronized progesterone (P) and of 0.5 mg of micronized estradiol (E2) were administered vaginally and orally, respectively, in the early follicular phase of the menstrual cycle in six premenopausal women. In the second cycle, the same doses were administered in the same subjects, orally for P and vaginally for E2. Serial blood samples were collected. P and E2 levels were higher after vaginal than after oral administration, while those of E1 (estrone) were similar after either route. Metabolites of P were higher after oral administration. Concerning estrogen sulfates, E1S concentrations were similar whichever the route, while those of E2S were lower after oral than after vaginal administration. The authors concluded that "in view of the metabolic pathways which are operative and of the peripheral plasma levels which were found, the vaginal route appears to be more adequate than the oral one for hormone replacement therapy."*

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*This study showed that transdermal estradiol and oral norethisterone reduce plasma triglyceride and total cholesterol levels, factor VII activity and vonWillebrand factor antigen levels in women with Type 2 diabetes without a concurrent change in adiposity or glycemic control. The authors suggest that this protocol might be of benefit for women at high risk of cardiovascular disease.*

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placebo-controlled study. *Journal of Clinical Endocrinology and Metabolism* 2000 Dec;85(12):4462-9.

*This study determined that oral low-dose estrogen (0.25mg/day) had similar beneficial effects on bone health in elderly (mean age 75 years) postmenopausal women without the breast tenderness and bleeding associated with higher doses. Authors recommended the use of serum E2 levels as the guide for therapeutic effect at a range of 10-28pg/L.*

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*This randomized, double blind, placebo-controlled trial looked at the incidence of urinary tract infections (UTI) in 93 postmenopausal women using 0.5 mg estriol vaginal cream once nightly for two weeks followed by twice weekly application or placebo. Results showed significantly lower UTI rates in treatment group (0.5 infections per patient-year vs. 5.9 for placebo group). The mean vaginal pH fell from 5.5+-0.7 to 3.6+-1.0 for treatment group and 5.8+-1/2 to 6.1+-2.0 in placebo group and there was an increase in vaginal colonization with lactobacilli in the treatment group. Authors recommend use of topical vaginal estriol in preventive treatment of women with frequent UTI as possible replacement for long-term use of nitrofurantoin, co-trioxazole, trimethoprim, cephalexin or fluoroquinolones.*

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*In a randomized, double-blind, placebo-controlled, crossover clinical trial of 31 postmenopausal women, average age 59.7 years, using 2.0mg of oral estradiol (E2) daily, the authors investigated the effects of estradiol on cardiac function and structure. This study did not include the use of progestins with estrogen. 12 weeks of E2 therapy showed no change in left ventricular thickness or mass, left atrial size or aortic size. There was a small but significant increase in left ventricular end-diastolic volume but it was not associated with change in end-systolic volume or ejection fraction changes. Heart rate and systolic and diastolic pressures were unchanged after 3 months of treatment. Time-velocity integral of flow and peak flow velocities were unaffected by E2 treatment. Authors concluded that estrogen replacement therapy did not affect cardiac structure or size in normal postmenopausal women (after 12 weeks of treatment).*

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*This randomized, double-blind, placebo-controlled trial investigated the efficacy of 17beta-estradiol for the treatment of clinically significant depressive disorders in 50 perimenopausal women (FSH >25 IU/L, irregular menses), meeting criteria for major depressive disorder, dysthymic disorder, or minor depressive disorder. Women received transdermal patches of 17beta-estradiol (100 microgram) or placebo for 12-weeks. A 4-week washout period followed the 12-week treatment phase. Outcome measures were the Montgomery-Asberg Depression Rating Scale and Blatt-Kupperman Menopausal Index scores. RESULTS: Remission of depression was observed in 17 (68%) women treated with 17beta-estradiol compared with 5 (20%) in the placebo group (P = .001). Subjects responded similarly to estradiol treatment, regardless of DSM-IV diagnosis. CONCLUSION: Transdermal estradiol replacement is an effective treatment of depression for perimenopausal women.*

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*This study looked at whether or not sublingual troche use of bioidentical estradiol, progesterone, testosterone, and DHEA raised serum levels. Each troche contained estradiol (0.5 mg), progesterone (200 mg), testosterone (2.0 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). Each of the hormones was readily absorbed via the buccal mucous membrane. Peak plasma*

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*concentrations of estradiol and progesterone were comparable to those found normally in young menstruating women.*

- Wise PM. Estradiol: a protective factor in the adult brain. *J Pediatr Endocrinol Metab* 2000;13 Suppl 6:1425-9.
- Wise P. Estradiol exerts neuroprotective actions against ischemic brain injury: insights derived from animal models. *Endocrine*. 2003 Jun;21(1):11-5.
- Yang TS, Tsan SH, Chang SP, Ng HT. Efficacy and safety of estriol replacement therapy for climacteric women. *Zhonghua Yi Xue Za Zhi ( Taipei )* 1995 May;55(5):386-91.
- 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.

*This study looked at short term (14 days) oral estriol (2.0mg/day) treatment for atrophic vaginitis in 59 postmenopausal women aged 50-75 years. The results showed that in the majority of women in the study group the oral estriol restored normal vaginal flora by the end of the treatment period.*

- Zegura B, Keber I, Sebestjen M, Borko E. Orally and transdermally replaced estradiol improves endothelial function equally in middle-aged women after surgical menopause. *Am J Obstet Gynecol*. 2003 May;188(5):1291-6.
- Zegura B, Keber I, Sebestjen M, Koenig W. Double blind, randomized study of estradiol replacement therapy on markers of inflammation, coagulation and fibrinolysis. *Atherosclerosis*. 2003 May;168(1):123-9.
- Zegura B, Keber I, Sebestjen M, Borko E. Orally and transdermally replaced estradiol improves endothelial function equally in middle-aged women after surgical menopause. *American Journal of Obstetrics and Gynecology*. 2003 May;188(5):1291-6.

*Forty-three surgically induced (6 weeks postop) menopausal women were randomly assigned in a double-blind study to 28 weeks of 2.0mg oral or 50mcg transdermal estradiol. Looking at blood flow through the brachial artery, flow-mediated dilation (ultrasound) in the oral group increased 6.0 to 13.2% and in the transdermal group increased 7.0 to 14.9% Results indicate that both oral and transdermal administration had equal effect on arterial endothelium independent of lipid profiles and increased vasodilation.*

#### **Bioidentical Progesterone and Breast Health:**

- Chang KJ, et al. Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. *Fertil Steril* 1995; 63(4):785-91.

*The effect of transdermal estradiol (1.5 mg), transdermal progesterone (25 mg), and combined transdermal estradiol and progesterone (1.5 mg and 25 mg) on human breast epithelial cell cycles was evaluated in vivo. Results demonstrated that estradiol significantly increases cell proliferation, while progesterone significantly decreases cell replication below that observed with placebo. Transdermal progesterone was also shown to reduce estradiol-induced proliferation.*

- Cowan LD, Gordis L, Tonascia JA, et al. Breast cancer incidence in women with a history of progesterone deficiency. *American Journal of Epidemiology* 1981; 114:209. ,083.

*Infertile women were followed for 14-34 years. Those who were deficient in progesterone showed a fivefold greater incidence of premenopausal breast cancer.*

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- Desreux J, Kebers F, Noel A, Francart D, Van Cauwenberge H, Heinen V, Thomas JL, Bernard AM, Paris J, Delansorne R, Foidart JM. Progesterone receptor activation- an alternative to SERMs in breast cancer. *Eur J Cancer* 2000 Sep;36 Suppl 4:S90-1.

*This review emphasizes progesterone's role in supporting healthy breast homeostasis and opposing the proliferative effects of estradiol in the breast, unlike synthetic progestins.*

- Flesch-Janys D, et al. Risk of different histological types of postmenopausal breast cancer by type and regimen of menopausal hormone therapy. *Int J Cancer*. 2008;123:933-941.
- Foidart JM, Colin C, Denoo X, Desreux J, Beliard A, Fournier S, de Lignieres B. Estradiol and progesterone regulate the proliferation of human breast epithelial cells. *Fertil Steril* 1998 May;69(5):963-9.

*In this double-blind randomized study, to evaluate the effects of estrogen and progesterone on normal breast cells, 40 postmenopausal women received daily topical application of a gel containing either placebo, estradiol, progesterone, or estradiol + progesterone for two weeks prior to esthetic breast surgery or the excision of a benign breast lesion. The results showed that increased estrogen concentration increased the number of cycling epithelial cells, whereas exposure to progesterone for 14 days reduced the estrogen-induced proliferation of normal breast epithelial cells.*

- Formby B, Wiley TS. Bcl-2, surviving and variant CD44 v7-v10 are downregulated and p53 is upregulated in breast cancer cells by progesterone: inhibition of cell growth and induction of apoptosis. *Mol Cell Biochem* 1999 Dec;202(1-2):53-61.

*This study sought to elucidate the mechanism by which progesterone inhibits the proliferation of breast cancer cells. Utilizing breast cancer cell lines with and without progesterone receptors (T47-D and MDA-231, respectively) in vitro, the authors looked at apoptosis (programmed cell death) in response to progesterone exposure as a possible mechanism. The genetic markers for apoptosis - p53, bcl-2 and surviving, were utilized to determine whether or not the cells underwent apoptosis. The results demonstrated that progesterone does produce a strong antiproliferative effect on breast cancer cell lines containing progesterone receptors, and induced apoptosis. The relatively high levels of progesterone utilized were similar to those seen during the third trimester of human pregnancy.*

- Formby B, Wiley TS. Progesterone inhibits growth and induces apoptosis in breast cancer cells: inverse effects on Bcl-2 and p53. *Ann Clin Lab Sci* 1998 Nov-Dec;28(6):360-9.

*This study explored the mechanism by which progesterone inhibits breast cancer cell proliferation (growth). In progesterone receptor positive T47-D breast cancer cells, the mechanism of apoptosis appeared to be through the regulation of the genes p53 and bcl-2 by progesterone. These genes control the apoptotic process. It was demonstrated that at progesterone levels that approximate the third trimester of pregnancy, there was a strong antiproliferative effect in at least 2 breast cancer cell lines.*

- Laidlaw IJ, Clarke RB. The proliferation of normal breast tissue implanted into athymic nude mice is stimulated by estrogen, but not by progesterone. *Endocrinology* Jan 1995;136(1):164-71.

*Normal human breast tissue was implanted subcutaneously into athymic nude mice. The mice were then treated with estradiol or progesterone such that serum levels approximated those seen in normal menstruating women. Immunocytochemical measures were made of proliferative activity and steroid receptor expression of the tissue implants. It was found that physiologic levels of estradiol significantly stimulated the proliferation of human breast epithelial cells and increased progesterone receptor expression 10-20-fold. Progesterone failed to affect proliferation alone or after estradiol priming.*

- Lin VC, Ng EH, Aw SE, Tan MG, Ng EH, Chan VS, Ho GH. Progestins inhibit the growth of MDA-MB-231 cells transfected with progesterone receptor complementary DNA. *Clin Cancer Res* 1999 Feb;5(2):395-

403.

*Progesterone is mainly thought to exert its effects via the estrogen-dependent progesterone receptor (PR), the effects of which may be overshadowed by the presence of estrogen. In order to study the independent effects of progesterone on breast cancer cell lines, PR expression vectors were transfected into a PR and ER negative cell line (MDA-MB-231). The growth of these cells was then studied in response to progesterone and several progestins. Progesterone was found to significantly inhibit DNA synthesis and cell growth in a dose-dependent fashion. The results of this study indicate that progesterone and progestins independent of estrogen have an antiproliferative effect on breast cancer cells via the progesterone receptor. This suggests a possible role in the treatment of PR negative breast cancer via re-activation of the PR receptor.*

- Malet C, Spritzer P, Guillaumin D, Kuttann F. Progesterone effect on cell growth, ultrastructural aspect and estradiol receptors of normal human breast epithelial (HBE) cells in culture. *J Ster Biochem Mol Biol* 2002; 73: 171-181.

*In a culture system, progesterone was found to have an inhibitory effect on breast cell growth. When given following estradiol (E2), it limited the stimulatory effect of E2 on cell growth.*

- Mauvais-Jarvis P, Kuttann F, Gompel A. Antiestrogen action of progesterone in breast tissue. *Horm Res* 1987;28(2-4):212-8.

*In a review of international literature on the cellular effects of progesterone on both normal breast cells and breast cancer cell lines, the authors conclude that most data indicate progesterone and progestins have an antiestrogenic effect on the breast, as reflected in the decrease in estradiol receptor content, the decrease in cell proliferation, and an increase in a marker of cell differentiation, 17 beta-hydroxysteroid activity, which is mediated by the progesterone receptor.*

- Mohr PE, Wang DY, Gregory WM, Richards MA, Fentiman IS. Serum progesterone and prognosis in operable breast cancer. *British Journal of Cancer* 1996;73:1532-1533.

*Higher blood levels of progesterone measured during surgical treatment of breast cancers were associated with significantly better survival, especially in women who were node-positive ( $P < 0.01$ ). There was no significant relationship between E2 levels and survival. This study demonstrated that a higher level of progesterone at time of excision is associated with improved prognosis in women with operable breast cancer.*

- Plu-Bureau G, Le MG, Thalabard JC, Sitruk-Ware R, Mauvais-Jarvis P. Percutaneous progesterone use and risk of breast cancer: results from a French cohort study of premenopausal women with benign breast disease. *Cancer Detect Prev* 1999;23(4):290-6.

*This cohort study followed 1150 premenopausal French women diagnosed with benign breast disease. Topical progesterone cream, a common treatment for mastalgia in Europe, had been prescribed to 58% of the women. Follow-up accumulated 12,462 person-years. There was no association noted between progesterone cream use and breast cancer risk. Furthermore, women who had used both progesterone cream and an oral progestogen had a significant decrease in breast cancer risk (RR= 0.5) as compared to women who did not use progesterone cream. There was no significant difference in the risk of breast cancer in percutaneous progesterone users versus nonusers among oral progestogen users. These results suggest there are no deleterious effects caused by percutaneous progesterone use in women with benign breast disease.*

#### **Progesterone and General Health:**

- Dalton K. Prenatal progesterone and educational attainments. *British Journal of Psychiatry* 1976; 126:438-42.

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*This study compares educational attainments of 34 children whose mothers received prenatal progesterone with 37 normal and 12 toxemic controls. Results at ages 17-24 showed that progesterone children were more likely to continue schooling after 16 years, a higher number left school with 'O' and 'A' level grades and more obtained entrance to university. The best academic results were found for children whose mothers had received over 5 grams of progesterone for a minimum of eight weeks, with treatment beginning before week sixteen.*

- Fitzpatrick LA, Pace C, Witta B. Comparison of regimens containing oral micronized progesterone or medroxyprogesterone acetate on quality of life in postmenopausal women: a cross-sectional survey. *J Womens Health Gend Based Med.* 2000;9(4):381-7.
- Mahesh VB, Brann DW, and Hendry LB. Diverse modes of action of progesterone and its metabolites. *J Steroid Biochem Molec Biol* 1996;56(1-6):209-219.

*A review of the actions of progesterone and its metabolites demonstrates physiological significance in such biological activities as may have importance in the regulation of stress, post-partum depression, memory, cognition, PMS, and depression, to name a few.*

- Nappi C, Affinito P. Double-blind controlled trial of progesterone vaginal cream treatment for cyclical mastodynia in women with benign breast disease. *J Endocrin Invest* 1994;15(11):801-6.

*Eighty regularly menstruating women with mastodynia were studied to evaluate the clinical effectiveness of vaginally administered micronized progesterone. Subjects were randomly assigned to one of two groups, with all participating in a control cycle prior to treatment. One group received 4 grams of vaginal cream containing 2.5% natural progesterone for six cycles from day 19 to day 25 of the cycle. The other group was similarly treated with placebo. Both subjective reporting on a daily basis and clinical examination revealed a significant reduction in breast pain, defined as 50% reduction, in 64.9% of subjects receiving progesterone and 22.2% of subjects receiving placebo. Effects of breast nodularity were not significant. No side effects were detected.*

- Sitruk-Ware R, Bricaire C, De Lignieres B, Yaneva H, Mauvais-Jarvis P. Oral micronized progesterone. Bioavailability pharmacokinetics, pharmacological and therapeutic implications--a review. *Contraception* 1987 Oct; 36(4): 373-402.

*This paper reviews the effects and benefits of oral micronized progesterone. Progesterone exhibits anti-estrogenic effects, anti-androgenic effects, and anti-mineralcorticoid effects in addition to its progestational effects. No side effects have been reported for micronized progesterone with respect to lipid profile, coagulation, or blood pressure, leading the authors to recommend micronized progesterone as suitable for treatment of PMS, menopause, irregular cycles, and pregnancy maintenance.*

- Sofuoglu M, Babb DA, Hatsukami DK. Progesterone treatment during the early follicular phase of the menstrual cycle: effects on smoking behavior in women. *Pharmacol Biochem Behav* 2001 May-Jun;69(1-2):299-304.

*In this unique randomized controlled study, administration of progesterone (200 mg oral) demonstrated a decrease in craving for and subjective effects of cigarette smoking in female smokers. With progesterone treatment, there was a noted trend to decrease smoking.*

### **Progesterone Safety**

Historically and unfortunately, progesterone and synthetic progestins have been lumped together with respect to their safety profiles, although the two hormones are vastly different in their molecular structure

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and effects. Further complicating the understanding of individual safety, early reports of concerns for progestins were not often separated from those of the combination hormone therapies they were a part of. In the last decade and increasingly since the pivotal Women's Health Initiative (WHI) study results of 2002, there has been heightened interest by researchers for elucidating the safety of progesterone – alone, in combination, and in contrast to synthetic progestins. This research suggests a good safety profile for progesterone with respect to the cardiovascular system, breasts, brain, and other target tissues. Numerous human studies evaluating progesterone reported the treatments were well tolerated, with few side effects.

**Ovaries:**

- Hu Z, Deng X. [The effect of progesterone on proliferation and apoptosis in ovarian cancer cell] *Zhonghua Fu Chan Ke Za Zhi* 2000 Jul;35(7):423-6. [Article in Chinese]

*In this in vitro study, researchers demonstrated that administered progesterone had a dose-dependent effect causing inhibition of growth of epithelial ovarian cancer cells, suggesting an anti-cancer effect.*

- Yu S, Lee M, Shin S, Park J. Apoptosis induced by progesterone in human ovarian cancer cell line SNU-840. *J Cell Biochem* 2001;82(3):445-51.

*Although the mechanism is not fully understood, progesterone has been used as an anticancer therapy for the treatment of ovarian cancer. This study evaluates the effects of progesterone on ovarian cancer cells (SNU-840). Following incubation with 100 microM progesterone, viability of the cancer cells was evaluated by MTT assay, resulting in 45% of the cells being viable after 48 h. Additionally, [(3)H] thymidine incorporation assay showed that progesterone completely inhibited the proliferation of the cells at the same duration and concentration. Cell death was by apoptosis as seen by fragmentation of the chromosomal DNA via colorimetric TUNEL assay. The level of the p53 mRNA reached its maximum at 12 h, then decreased following incubation with progesterone as determined by northern blotting assay. This is consistent with the fact that many apoptosis processes are mediated by up-regulation of the p53 expression. The authors conclude that progesterone inhibits the proliferation of and elicits apoptosis of the SNU-840 line of ovarian cancer cells and up-regulates p53 expression.*

**General Safety:**

- Arafat ES, Hargrove JT, Maxson WS, Desiderio DM, Wentz AC, Andersen RN. Sedative and hypnotic effects of oral administration of micronized progesterone may be mediated through its metabolites. *Am J Obstet Gynecol* 1988 Nov; 159(5): 1203-9.

*This small pilot study evaluated progesterone and its metabolites following administration of oral micronized progesterone in eight postmenopausal women. Progesterone and its metabolites were measured in serum extracts by radioimmunoassay and gas chromatography-massspectrometry. Evaluation of serial blood samples showed elevated levels of serum progesterone and its metabolites from baseline, reaching a peak between 2 and 6 hours after oral administration. The following compounds: progesterone, 5 beta-pregnan-3 alpha, 5 alpha-pregnan-3 alpha-ol-20-one, 5 beta-pregnan-3 alpha-ol-20-one, 20 beta-diol, and 5 beta-pregnan-3 alpha-ol-11,20-dione, were identified. These compounds have reported anesthetic qualities, which may contribute to the sedative and hypnotic effects seen with oral administration of progesterone. The authors reported that, in one subject, 400 mg of oral micronized progesterone induced a hypnotic state lasting approximately 2 hours.*

- Burry KA, Patton PE, Hermsmeyer K. Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen. *Am J Obstet Gynecol* 1999 Jun;180(6 Pt 1):1504-11.

*This pilot study demonstrated a significant increase in serum progesterone levels in 6 women receiving topical progesterone cream (Pro-gest®; 30-60 mg P4/day) and 17beta estradiol (0.05mg patch). The*

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*absorption of progesterone via a topical cream correlated well with estrogen absorption ( $p < 0.001$ ). They concluded that progesterone cream appeared to be a safe and effective route of application.*

- de Wit H, Schmitt L, Purdy R, Hauger R. Effects of acute progesterone administration in healthy postmenopausal women and normally-cycling women. *Psychoneuroendocrinology* 2001 Oct;26(7):697-710.

*This randomized controlled study investigated the effects of acute progesterone administration (25, 50, 100 mg, intramuscularly, 1 dose/wk) on mood. Contrary to the investigators' expectations, very few unwanted behavioral effects were noted, and only in the highest dose (100 mg) did women slightly increase their self-rating of "sluggishness".*

- Darj E, Axelsson O, et al. Liver Metabolism During Treatment with Estradiol and Natural Progesterone. *Gynecological Endocrinology* June 1993; 7(2):111-4.

*Thirty postmenopausal women were treated daily for four months with 2 mg micronized 17 beta-estradiol and micronized progesterone orally in doses of 50, 100 and 200 mg daily. Serum concentrations of sex hormone-binding globulin (SHBG), corticosteroid binding globulin (CBG), ceruloplasmin, lipoprotein A and liver enzymes were measured. Serum SHBG and CBG increased during treatment with a weak association shown between progesterone and serum CBG. Levels of lipoprotein A and liver enzymes did not change, concluding that natural progesterone supplementation in postmenopausal women does not appear to cause any side effects to the liver.*

- de Ziegler D, Fanchin R. Progesterone and progestins: applications in gynecology. *Steroids* 2000 Oct-Nov;65(10-11):671-9.

*This paper reviews the use of a transvaginal progesterone gel as a viable option to other routes of application of natural progesterone (intramuscular, oral micronized), and offered it as a viable option to synthetic progestins given the low incidence of side effects noted in existing studies.*

- Fitzpatrick LA, Good A. Micronized progesterone: clinical indications and comparison with current treatments. *Fertil Steril* 1999 Sep;72(3):389-97.

*The literature reviewed in this tutorial indicates a potential use for oral micronized progesterone for the treatment of secondary amenorrhea, dysfunctional uterine bleeding, luteal phase disorders, premenopausal bleeding disorders, and as a component of hormone replacement therapy that may provide a better safety profile than commonly utilized synthetic progestins.*

- Horita K, Inase N, Miyake S, Formby B, Toyoda H, Yoshizawa Y. Progesterone induces apoptosis in malignant mesothelioma cells. *Anticancer Res* 2001 Nov-Dec;21(6A):3871-4.

*In this study, researchers demonstrated that progesterone administration suppressed cell proliferation and induced apoptosis (programmed cell death) in malignant mesothelioma cells (21 1H). This is consistent with an earlier in vitro study that found administered progesterone induced apoptosis in the breast cancer cell line, T47-D.*

- Shantha S, Brooks-Gunn J, Locke RJ, Warren MP. Natural vaginal progesterone is associated with minimal psychological side effects: a preliminary study. *J Women Health Gend Based Med* 2001 Dec;10(10):991-7.

*This 3 month, multicenter randomized study evaluated the psychological side effects of a vaginally applied progesterone gel in reproductive aged women treated for hypothalamic amenorrhea or premature ovarian failure. No differences were noted in psychometric measures as evaluated by the Hopkins Symptom Checklist. Natural progesterone in a vaginal gel can be an effective treatment for women requiring hormone therapy.*

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- Sitruk-Ware R, Bricaire C, De Lignieres B, Yaneva H, Mauvais-Jarvis P. Oral micronized progesterone. Bioavailability pharmacokinetics, pharmacological and therapeutic implications--a review. *Contraception* 1987 Oct; 36(4): 373-402.

*This paper reviews the effects and benefits of oral micronized progesterone. Progesterone exhibits anti-estrogenic effects, anti-androgenic effects, and anti-mineralcorticoid effects in addition to its progestational effects. No side effects have been reported for micronized progesterone with respect to lipid profile, coagulation, or blood pressure, leading the authors to recommend micronized progesterone as suitable for treatment of PMS, menopause, irregular cycles, and pregnancy maintenance.*

**Research on Progesterone and PMS:**

- Dennerstein L, Spencer-Gardner C, Gotts G, Brown JB, Smith MA, Burrows GD. Progesterone and the premenstrual syndrome: a double blind crossover trial. *Br Med J (Clin Res Ed)* 1985 Jun 1; 290(6482): 1617-21.

*In this double-blind, placebo-controlled randomized crossover trial, oral micronized progesterone demonstrated effectiveness in alleviating premenstrual complaints. Twenty-three women completed a Beck, et al depression inventory, Moos's menstrual distress questionnaire, Spielberger, et al state anxiety inventory, and daily symptom diary before and during each treatment. There was an overall benefit of treatment for all variables, except positive moods, restlessness, and interest in sex. For most parameters, maximum benefit was seen within the first month of treatment, demonstrating an effectiveness of progesterone as a viable treatment option for women with PMS.*

- Magill PJ. Investigation of the efficacy of progesterone pessaries in the relief of symptoms of premenstrual syndrome. Progesterone Study Group. *Br J Gen Pract* 1995 Nov; 45(400): 589-93.

*This multi-center, prospective, double-blind, randomized parallel study undertook to compare progesterone vaginal suppositories (400 mg twice daily) with placebo for the relief of premenstrual symptoms. Ninety-three participants completed the study. A clinically and statistically significant reduction of symptoms was consistently demonstrated in the women receiving the suppositories who had experienced symptoms in the moderately to severe categories. Adverse events were slightly higher in the active group (51 vs. 43%) and were limited to headache, irregular bleeding, and vaginal itching.*

**Research on Progesterone and Bone Health:**

- Lee JR. Osteoporosis reversal; the role of progesterone. *International Clinical Nutrition Review* 1990;10(3):384-91.

*Transdermal progesterone supplementation with and without conjugated estrogens was evaluated in a clinical setting using 100 women aged 38 to 83 years. The average time from onset of menopause was 16 years. 63 women were followed for three years with dual photon absorptiometry. Treatment also included dietary changes, nutritional supplements, and exercise. All individuals followed showed an increase in bone mineral density over the three years, with the greatest increase occurring in the first year. There was no difference noted between estrogen/progesterone and progesterone only groups. Subjective changes included increased libido, diminished hot flushes, reduced joint pain, and increased mobility and energy. No side effects were noted during treatment protocol.*

- Liang M, Liao EY, Xu X, Luo XH, Xiao XH. Effects of progesterone and 18-methyl levonorgestrel on osteoblastic cells. *Endocr Res* . 2003 Nov;29(4):483-501.

*The authors evaluated in this study the effects of progesterone (P4) and levonorgestrel (LNG) on markers of bone growth, utilizing normal human osteoblasts as well as the osteosarcoma cell line, MG-*

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63. Their study found that, compared with placebo, both P4 and LNG increased the proliferation and differentiation of human osteoblasts through osteocalcin gene transcription.

- Prior JC, Vigna Y, Alojado N. Progesterone and the prevention of osteoporosis. *Canadian Journal of Obstetrics/Gynecology and Women's Health Care* 1991; 3(4):178-84.

*In this review article, the authors propose that cyclic progesterone both prevents bone loss and acts as a bone-builder. The studies discussed focus on abnormal menstrual cycles as an important risk factor for osteoporotic fractures. Their conclusion is that the first step in preventing osteoporosis is treating ovulation disorders.*

- Prior JC. Progesterone as a bone-trophic hormone. *Endocrine Reviews* 1990;11(2): 386-398.
- Prior JC, Vigna YM, Schecter MI, Burgess AE. Spinal bone loss and ovulatory disturbances. *New England Journal of Medicine* 1990; 323:1221-7. A review of the available data indicates that progesterone acts to promote bone metabolism. It appears to be independent of estrogen by either acting directly at progesterone receptors, or indirectly through competition at glucocorticoid receptors in the osteoblasts.

**Research on Bioidentical Progesterone and Fertility and Pregnancy:**

- Ferre F, Uzan M, Janssens Y, Tanguy G, Jolivet A, Breuiller M, Sureau C, Cedard L. Oral administration of micronized natural progesterone in late human pregnancy. Effects on progesterone and estrogen concentrations in the plasma, placenta, and myometrium. *Am J Obstet Gynecol* 1984 Jan 1; 148(1): 26-34.

*Levels of progesterone, 17 beta-estradiol, and estrone were measured in the plasma, in the placenta, and at different sites in myometrium following a single dose of micronized oral progesterone administered to 15 pregnant women immediately prior to elective cesarean section. In comparison to a control group, progesterone levels in the treated women increased in the plasma and myometrium 150 minutes after administration. Placenta progesterone levels did not demonstrate any change. No change was seen in 17 beta-estradiol levels in the plasma or the myometrium, however placental levels were increased. Estrone levels were decreased in the myometrium and in the placenta, and unchanged in the plasma.*

- Hajek Z, Uhlir M. [Micronized progesterone in the treatment of imminent necrosis of a myoma during pregnancy. Ultrasound changes during treatment] *Ceska Gynekol* 1999 Jun;64(3):189-92. [Article in Czech]

*Progesterone has a role in increasing blood flow to the uterus during pregnancy. As such, these researchers studied the effect of progesterone treatment to resolve imminent necrosis of a myoma in two cases. Both resolved within several days following oral and vaginal doses of progesterone (300-600 mg/day). Both women went on to deliver healthy, full-term infants.*

- Lydon JP, DeMayo FJ, Conneely OM, and O'Malley BW. Reproduction phenotypes of the progesterone receptor null mutant mouse. *J Steroid Biochem Molec Biol* 1996; 56(1-6):67-77.

*In an attempt to better understand the diversity of progesterone's effects, a novel mouse strain homozygous for the absence of progesterone receptors has been studied. Female PR null mice were found to have extensive reproductive abnormalities, and results provide evidence for progesterone's diverse role as the coordinator of events that ensure female fertility. Future studies of this animal model may help redefine progesterone's role as not just a sex steroid, but as a key player and regulator in a variety of physiological processes.*

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- Massai R, Miranda P, et al. Preregistration study on the safety and contraceptive efficacy of a progesterone-releasing vaginal ring in Chilean nursing women. *Contraception* 1999 Jul;60(1):9-14.

*In this long-term controlled study, the safety and efficacy of a progesterone-releasing vaginal contraceptive device was compared to that of the copper-T 380A IUD in nursing mothers. There was no difference in breastfeeding performance or infant growth between groups. The participants using the progesterone-releasing ring had a longer period of lactational amenorrhea than did the group using the copper T. Women were tracked for over 2000 women-months of exposure in both groups. The Chilean government found the progesterone-releasing ring to be a safe and effective contraceptive alternative.*

- Pouly JL, Bassil S, Frydman R, et al. Luteal support after in-vitro fertilization: Crinone  $\dot{O}$ , a sustained release vaginal progesterone gel, versus Utrogestan  $\dot{O}$ , an oral micronized progesterone. *Human Reprod* 1996;11:2085-89.

*90 mg of vaginal estrogen gel daily was compared to 300 mg oral progesterone daily in a randomized open-label trial of 283 IVF patients. Delivery rates, safety parameters, frequency of spontaneous abortion, ratio of newborn babies to embryo transfer were nearly identical for both groups. The oral progesterone group reported more drowsiness.*

#### **Research on Bioidentical Progesterone and Heart Health:**

- Carmody BJ, Arora S, Wakefield MC, Weber M, Fox CJ, Sidawy AN. Progesterone inhibits human infragenicular arterial smooth muscle cell proliferation induced by high glucose and insulin concentrations. *J Vasc Surg* 2002 Oct;36(4):833-8.

*In vitro, progesterone was shown to have antiproliferative effects on vascular smooth muscle after proliferation was induced by models simulating hyperinsulinemia and hyperglycemia. Progesterone may, therefore, have a protective role against the atherosclerotic changes seen with diabetes (type II).*

- Cheng W, Lau OD, Abumrad NA. Two antiatherogenic effects of progesterone on human macrophages; inhibition of cholesteryl ester synthesis and block of its enhancement by glucocorticoids. *J Clin Endocrinol Metab* 1999 Jan;84(1):265-71.

*This study evaluated the effects of estradiol and progesterone on cholesteryl ester(CE) formation. Progesterone blocked CE formation, while estradiol had no effect. In comparison, cortisol and prednisolone (a widely prescribed glucocorticoid) both increased CE formation from 2-fold to 5-fold. This study demonstrated a role for progesterone in the decrease of cardiovascular risk factors that was not mediated by the progesterone receptor.*

- Hermsmeyer RK, Mishra RG, Pavcnik D, Uchida B, Axthelm MK, Stanczyk FZ, Burry KA, Illingworth DR, Juan C, Nordt FJ. Prevention of coronary hyperreactivity in preatherogenic menopausal rhesus monkeys by transdermal progesterone. *Arterioscler Thromb Vasc Biol* . 2004 May;24(5):955-61.

*Previous studies by Hermsmeyer, et al demonstrated a reduction of coronary reactivity in response to subphysiological levels of progesterone in non-atherogenic monkeys. In this study, the authors sought to determine if transdermal progesterone cream conferred coronary vascular protection in surgically menopausal preatherosclerotic rhesus monkeys. Compared with monkeys receiving placebo cream (n= 5), treated monkeys (n= 7) experienced reduced Lp (a) levels, and an attenuation of coronary vasoconstriction, which was artificially stimulated by intracoronary serotonin plus U46619. Coronary hyperreactivity is a component of coronary artery disease and was demonstrated in this study to be prevented in preatherosclerotic primates by progesterone cream treatment.*

- Lee WS, Harder JA, Yoshizumi M, Lee ME, Haber E. Progesterone inhibits arterial smooth muscle cell proliferation. *Nat Med* 1997 Sep;3(9):1005-8.

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*Premenopausal women have a lower mortality from atherosclerotic cardiovascular disease than age-matched men. Progesterone receptors have been found in human and rat aortic smooth muscle cells in vivo and in vitro. This study examined the effect of progesterone on the proliferation of vascular smooth muscle cells. At physiologic levels, progesterone dose-dependently inhibited DNA synthesis and proliferation. RU486, a progesterone antagonist, blocked inhibition. This inhibition of arterial smooth muscle suggests a protective effect of progesterone against atherosclerosis.*

- Molinari C, Battaglia A, Grossini E, Mary DA, Surico N, Vacca G. Effect of progesterone on peripheral blood flow in prepubertal female anesthetized pigs. *J Vasc Res* 2001 Nov-Dec;38(6):569-77.

*To determine the effects of progesterone on the peripheral circulation, prepubertal female pigs were anesthetized with sodium pentobarbitone and changes in the superior mesenteric, left renal and left external iliac flow caused by intravenous infusion of progesterone were assessed using electromagnetic flow meters. Increased blood flows in the mesenteric, renal, and iliac arteries were demonstrated in all 20 subjects. In 4 additional subjects, a dose dependent effect was noted. This effect was blocked by the injection of N(omega)-nitro-L-arginine methyl ester. Results demonstrated a vasodilatory effect of progesterone, with the mechanism being that of nitric oxide release.*

- Otsuki M, Saito H, Xu X, Sumitani S, Kouhara H, Kishimoto T, Kasayama S. Progesterone, but not medroxyprogesterone, inhibits vascular cell adhesion molecule-1 expression in human vascular endothelial cells. *Arterioscler Thromb Vasc Biol* 2001 Feb;21(2):243-8.

*This study utilizing human umbilical vein endothelial cells (HUVEC's) demonstrated that progesterone, but not medroxyprogesterone acetate (MPA) inhibited expression of vascular cell adhesion molecule-1 (VCAM-1), demonstrating a role for progesterone in the prevention of atherosclerosis. The differing effects of progesterone and MPA are clinically important, as MPA is widely used in hormone replacement therapy, when, as this research suggests, progesterone might be a more appropriate option.*

- Rosano GM, Webb CM, Chierchia S, Morgani GL, Gabraele M, Sarrel PM, de Ziegler D, Collins P. Natural progesterone, but not medroxyprogesterone acetate, enhances the beneficial effect of estrogen on exercise-induced myocardial ischemia in postmenopausal women. *J Am Coll Cardiol* 2000 Dec;36(7):2154-9.

*This randomized crossover study compared the effects of estradiol (E2) (2mg/day), estradiol + progesterone (P4) vaginal gel (2 mg/day + 90 mg on alternate days), and estradiol + medroxyprogesterone acetate (MPA) (2 mg/day + 10 mg/day) on exercise-induced myocardial ischemia in eighteen postmenopausal women with coronary artery disease (CAD) or previous myocardial infarction (MI). Utilizing treadmill testing, patients were evaluated for exercise tolerance after each estradiol phase and at day 10 of each progestogen phase. The results demonstrated an increase in exercise tolerance with both E2 and E2 + progesterone, but not by E2 + MPA as compared to baseline. Furthermore, E2 + P4 demonstrated a significant increase in exercise tolerance when compared to MPA. The results suggest that progesterone may be the progestogen of choice for hormone replacement therapy for women at risk for cardiovascular disease.*

- Rylance PB, Brincat M, Lafferty K, De Trafford JC, Brincat S, Parsons V, Studd JW. Natural progesterone and antihypertensive action. *Br Med J (Clin Res Ed)* 1985 Jan 5;290(6461):13-4.

*In a placebo controlled, double blind crossover study, increasing doses of natural progesterone was given orally to six men and four postmenopausal women with mild to moderate hypertension who were not receiving any other antihypertensive drugs. Compared to before treatment values and to 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. The authors suggest this protective effect of progesterone should be investigated further.*

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- Tsuda K, Kinoshita Y, Nishio I. Synergistic role of progesterone and nitric oxide in the regulation of membrane fluidity of erythrocytes in humans: an electron paramagnetic resonance investigation. *Am J Hypertens* 2002 Aug;15(8):702-8

*Progesterone increased red blood cell membrane fluidity in this in vitro study, in part by a nitric oxide-dependent mechanism. It has been demonstrated that progesterone may play various roles in the regulation of blood pressure and other cardiovascular activities. The findings of this study suggest a positive role for progesterone in the improvement of microcirculation in humans.*

- Bagis T, Gokcel A, Zeyneloglu HB, Tarim E, Kilicdag EB, Haydardedeoglu B. The effects of short-term medroxyprogesterone acetate and micronized progesterone on glucose metabolism and lipid profiles in patients with polycystic ovary syndrome: a prospective randomized study. *J Clin Endocrinol Metab* 2002 Oct;87(10):4536-40.

*This randomized prospective study evaluated and compared the effects of ten days treatment with oral and vaginal progesterone (MP) and medroxyprogesterone acetate (MPA) on glucose metabolism, lipid profiles, and hormonal parameters in 28 patients with polycystic ovary syndrome (PCOS). Oral MPA and oral MP decreased LH ( $P = 0.028$ ,  $P = 0.009$ , respectively) and total testosterone ( $P = 0.013$ ,  $P = 0.037$ , respectively) levels. There was no change in hormonal parameters with vaginal MP. Basal insulin decreased ( $P = 0.021$ ) and insulin sensitivity increased significantly in the oral MPA group. Low density lipoprotein cholesterol (LDL) and lipoprotein (a) levels decreased only in the MPA group. This study concluded that MPA and oral MP may reduce insulin sensitivity in patients with PCOS. Vaginal MP had no effect on glucose metabolism and lipid profiles.*

- Bolaji II, Grimes H, Mortimer G, Tallon DF, Fottrell PF, O'Dwyer EM. Low-dose progesterone therapy in oestrogenised postmenopausal women: effects on plasma lipids, lipoproteins and liver function parameters. *Eur J Obstet Gynecol Reprod Biol* 1993 Jan;48(1):61-8.

*This 12 month prospective, open, non-comparative study measured the effects progesterone (oral micronized 100mg/day) paired with 0.625 mg conjugated equine estrogens (CEE) and found progesterone had no adverse effects on the lipid profile when combined with CEE. This lack of effect differs from other studies that noted adverse effects on lipid profiles when synthetic progestins were utilized with CEE.*

- Hargrove JT, Maxson WS, Wentz AC, Burnett LS. Menopausal hormone replacement therapy with continuous daily oral micronized estradiol and progesterone. *Obstetrics & Gynecology* April 1989; 73(4): 606-12.

*Fifteen menopausal subjects were studied to determine the efficacy and safety of hormone replacement therapy with micronized estradiol (E2) and progesterone. Ten subjects were given 0.7-E2 (1.05 mg daily) and progesterone (200-300 mg daily) and evaluated over one year at month 0, 1, 3, 6 and 12. Five subjects were administered conjugated estrogens (0.625mg daily) and medroxyprogesterone acetate (10 mg daily) and evaluated at the same intervals. Results showed all 10 women on E2 and progesterone had a decrease in total cholesterol with an increase in HDLs and sustained amenorrhea with no endometrial hyperplasia or withdrawal bleeding after six months of observation. Four of five women in the conjugated estrogen group continued to have withdrawal bleeding without endometrial hyperplasia. HDLs also increased in this group but no significant change in total cholesterol was found.*

- Mather KJ, Norman EG, Prior JC, Elliott TG. Preserved forearm endothelial responses with acute exposure to progesterone: A randomized cross-over trial of 17-beta estradiol, progesterone, and 17-beta estradiol with progesterone in healthy menopausal women. *J Clin Endocrinol Metab* 2000 Dec;85(12):4644-9.

*Regularly menstruating women enjoy relative protection from cardiovascular disease. Until recently, this has been attributed to the function of estrogen, despite the fact that progesterone is also present. This*

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*study evaluated the differing acute effects of 17-beta estradiol with and without progesterone with progesterone alone on endothelial function in a randomized crossover trial. Endothelial function was evaluated via endothelium dependent and independent forearm blood flow (FBF) using venous occlusion plethysmography. Flow responses were measured during brachial artery infusions achieving physiological levels of E2, E2 + P4, or P4 respectively along with either acetylcholine (an endothelium-dependent vasodilator), or sodium nitroprusside (an endothelium-independent vasodilator) in 27 healthy menopausal women with no cardiovascular disease risk factors. Small, statistically non-significant increases in endothelium-dependent flow responses were seen with all treatments. No impairment in response was seen with P4 alone or in combination with E2. The authors concluded that progesterone does not have detrimental vascular effects in humans.*

- Ottosson UB, Johansson BG, et al. Subfractions of high-density lipoprotein cholesterol during estrogen replacement therapy: A comparison between progestogens and natural progesterone. *American Journal of Obstetrics and Gynecology* 1993 Mar;151(6): 746-50.

*Fifty-eight postmenopausal women were followed with respect to subfractions of high-density lipoprotein during 3 cycles of unopposed estrogen. The women received either levonorgestrel, medroxyprogesterone acetate, or natural progesterone during the last ten days of the treatment period. Both progestogens significantly lowered HDL cholesterol, whereas natural progesterone had no effect on HDL levels.*

- Rosano GM, Webb CM, Chierchia S, Morgani GL, Gabraele M, Sarrel PM, de Ziegler D, Collins P. Natural progesterone, but not medroxyprogesterone acetate, enhances the beneficial effect of estrogen on exercise-induced myocardial ischemia in postmenopausal women. *J Am Coll Cardiol* 2000 Dec;36(7):2154-9

*Eighteen postmenopausal women were randomized to receive 17-beta estradiol with a synthetic progestin (medroxyprogesterone acetate) or a progesterone vaginal gel for 4 weeks, then crossed over to the alternate treatment. Researchers found through treadmill testing that estrogen plus progesterone significantly increased exercise time before myocardial ischemia, when compared to estradiol plus synthetic progestin. In addition, 2 patients on the synthetic progestin arm had to discontinue due to unstable angina. This research suggests that women at risk for cardiovascular disease need to consider progesterone as a safer alternative to synthetic progestins as a part of their hormone replacement therapy regime.*

- Saarikoski S, Yliskoski M, Penttila I. Sequential use of norethisterone and natural progesterone in premenopausal bleeding disorders. *Maturitas* 1990 Jun;12(2):89-97.

*This randomized controlled study evaluated the effects of norethisterone (NET) and micronized progesterone (MP) on bleeding disorders in pre-menopausal women. 80 patients were randomized to the trial and all were found via endometrial morphology to need progestogen therapy. They were subsequently treated with NET or MP. In both treatment groups, hyperplastic changes disappeared during the first three cycles, with the duration of treatment being 6 months. NET decreased follicle-stimulating hormone, luteinizing hormone, estradiol and sex-hormone-binding globulin levels ( $P < 0.001$ ) whereas no changes were seen during MP treatment. High-density-lipoprotein cholesterol and triglyceride levels were also lowered by NET ( $P < 0.001-0.02$ ) slightly decreased phospholipids. MP treatment had no effect on lipid profiles suggesting it may be a preferred progestogen for the treatment of bleeding disorders. Sitruk-Ware R. Progestins and cardiovascular risk markers. *Steroids* 2000 Oct-Nov;65(10-11):651-8. This article reviews the effects of various synthetic progestins and progesterone on cardiovascular health. Many synthetic progestins, especially 19-nortestosterone and some 17-hydroxyprogesterones, have negative effects on cardiovascular risk factors, whereas natural progesterone does not. Further studies utilizing natural and other steroids should be considered.*

- Burry KA, Patton PE, Hermsmeyer K. Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen. *Am J Obstet Gynecol* 1999;180: 1504-1511

**Research on Bioidentical Progesterone and Menopausal Symptoms:**

- Fitzpatrick LA, Pace C, Wiita B. Comparison of regimens containing oral micronized progesterone or medroxyprogesterone acetate on quality of life in postmenopausal women: a cross-sectional survey. *J Women Health Gend Based Med* 2000 May;9(4):381-7.

*A cross-sectional survey was conducted to examine quality of life (QOL) related to physiological, somatic, and vasomotor effects of switching progestogen treatment from medroxyprogesterone acetate (MPA) to micronized progesterone in postmenopausal women already using hormone replacement therapy (HRT). One hundred seventy-six women who were currently using hormone replacement therapy (HRT) containing micronized progesterone for 1-6 months and had previously received HRT containing MPA were surveyed to assess QOL. Women using micronized progesterone-containing HRT experienced significant improvement in vasomotor symptoms, anxiety, somatic complaints and depressive symptoms. Women reported improved control of menopausal symptoms and perceptions of their vaginal bleeding patterns while on the micronized progesterone-containing regimen. Approximately 80% of women reported satisfaction with the progesterone-containing therapy. A micronized progesterone-containing HRT therapy offers the potential for improved QOL with respect to menopausal symptoms.*

- Leonetti HB, Longo S, Anasti JN. Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss. *Obstet Gynecol* 1999 Aug;94(2):225-8.

*In this randomized controlled trial, 102 menopausal women were treated with topical progesterone (Pro-Gest®, 20 mg daily) or placebo and monitored for 1 year. Improvement in vasomotor symptoms was seen in 83% of the women in the treatment group who had experienced hot flashes, compared to 19% in the placebo group ( $p < .001$ ). There was no difference noted in bone mineral densities between groups after one year. All women studied received a daily multivitamin and 1200 mg calcium.*

- Stephenson, Kenna; Price, Carol; Kurdowska, Anna; et al. Topical progesterone cream does not increase thrombotic and inflammatory factors in postmenopausal women. Session Type: "Publication Only" *Blood* 2004 Nov;104(11).

*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 increase thrombotic events in large prospective clinical trials including HERS I, and the 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, the authors 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-1, CRP, TNF $\alpha$ , and IL-6.*

*For subjects receiving 20 mg of topical progesterone cream for 4 weeks, Greene Climacteric Scale*

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*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 $\alpha$  and IL-6 also remained unchanged.*

*The authors conclude that 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 may be seen as an effective and safe alternative clinical therapy for women suffering from menopausal symptoms.*

- Wetzell W. Micronized progesterone: a new option for women's health care. *Nurse Pract* 1999 May;24(5):62-6, 71, 75-6.

*This paper discusses the use of micronized progesterone as a safe, effective, and well-tolerated therapy and reviews indications for use. It also includes case studies and issues of patient compliance and the need for an individualized treatment plan for women receiving hormone therapy.*

- Wren BG, Champion SM, Manga RZ, et al. Transdermal progesterone and its effect on vasomotor symptoms, blood lipid levels, bone metabolic markers, moods, and quality of life for postmenopausal women. *Menopause* 2003;10(1): 13-18.

### **Sleep**

- Montplaisir J, Lorrain J, Denesle R, Petit D. Sleep in menopause: differential effects of two forms of hormone replacement therapy. *Menopause* 2001; 8(1):10-16.

*This randomized clinical trial compared the effects of conjugated equine estrogen (CEE) and medroxyprogesterone acetate to CEE and oral micronized progesterone. Twenty-one postmenopausal women were studied in a sleep lab, with results demonstrating an improvement in subjective measures of menopausal symptoms and sleep in both groups. The group receiving natural progesterone had significantly improved sleep efficiency, whereas the medroxyprogesterone acetate group did not, suggesting that the former might better improve sleep in postmenopausal women.*

### **Quality of Life**

- Ryan N, Rosner A. Quality of life (QOL) and costs associated with micronized progesterone and medroxyprogesterone acetate in hormone replacement therapy for non-hysterectomized, postmenopausal women. *Clin Ther* 2001 Jul;23(7):1099-115.

*This prospective, multicenter, randomized, parallel-group study enrolled 182 postmenopausal women 45 to 65 years of age and evaluated the quality of life and menopausal symptoms associated with the use of medroxyprogesterone acetate vs oral micronized progesterone when used as a part of a regular hormone replacement therapy. Menopausal symptoms improved in both groups from baseline to 9 months, as did QOL measures. In addition, patients using micronized progesterone had specific improvements in the areas of cognition and menstrual problems whereas the patients using MPA did not. Micronized progesterone was seen as an effective, cost-comparable alternative to MPA as well as being better tolerated.*

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- Sherwin BB. Progestogens used in menopause. Side effects, mood and quality of life. *J Reprod Med* 1999 Feb;44(2 Suppl):227-32.

*This review summarizes the effects of progesterone on mood and other brain functions. Progesterone receptors are present in many of the same areas of the brain as estrogen receptors, including the limbic system and hypothalamus. The limbic system plays a prominent role in regulating mood and emotion. As a comparison, progesterone decreases brain excitability, while estrogens increase it. This relates to why women with epilepsy have a higher frequency of seizures during the part of the cycle when estrogen levels are high, and a reduced frequency when progesterone levels are high. Estrogen and progesterone may also have differing effects on MAO, thereby affecting concentration of serotonin (a mood elevator) in the brain.*

**Progesterone and the Nervous System, Brain, and Mood:**

- Baulieu E, Schumacher M. Progesterone as a neuroactive neurosteroid, with special reference to the effect of progesterone on myelination. *Steroids* 2000 Oct-Nov;65(10-11):605-12.

*This paper reviews the effects of progesterone on the brain, with special focus on its role in the formation of the myelin sheath surrounding nerve fibers. Other roles of progesterone in the brain include activating GABA receptors, which induces a calming effect.*

- Cummings JA, Brizendine L. Comparison of physical and emotional side effects of progesterone or medroxyprogesterone in early postmenopausal women. *Menopause* 2002 Jul-Aug;9(4):253-63.

*Twenty-three early postmenopausal women were randomized to either medroxyprogesterone acetate (MPA) or oral micronized progesterone combined with conjugated equine estrogens (CEE) and followed for 91 days in a sequence of treatments. None of the hormone treatments had any noticeable effect on mood. Participants using MPA experienced more breast tenderness and bleeding than those using progesterone. This study debunks the belief that progesterone depresses mood in healthy individuals.*

- Gibson CL, Murphy SP. Progesterone enhances functional recovery after middle cerebral artery occlusion in male mice. *J Cereb Blood Flow Metab.* 2004 Jul;24(7):805-13.

*Differences in outcomes following ischemia have been noted in the sexes, and is thought to be attributed to sex steroids. This study investigated the potential benefits of progesterone administration after focal cerebral ischemia of the middle cerebral artery of male mice. Male mice undergoing 60-minute middle cerebral artery occlusion (MCAO) received either progesterone or vehicle following occlusion. The mice receiving progesterone had significantly reduced lesion volume ( $p < 0.05$ ) when compared with the vehicle treated mice (control). Progesterone treatment also improved survival rate, weight recovery, and motor ability when compared to the control group. In addition, mice treated with progesterone demonstrated motor ability comparable to mice that did not undergo MCAO. The authors suggest the need to further investigate the mechanisms of progesterone action on recovery from cerebral injury.*

- Grossman KJ, Goss CW, Stein DG. Effects of progesterone on the inflammatory response to brain injury in the rat. *Brain Res.* 2004 May 15;1008(1):29-39.

*Progesterone has a known anti-inflammatory effect. In this study, male rats treated with progesterone (4 mg/kg) and/or vehicle, were examined with respect to cellular inflammatory response to frontal cortex injury on postsurgical days 1, 3, 5, 7 and 9. The treated mice suffered significantly less edema than untreated mice, as well as showed an increase in the accumulation of activated microglia, demonstrating a neuroprotective effect on the rat brain.*

- Schumacher M, Guennoun R, Robert F, Carelli C, Gago N, Ghomari A, Gonzalez Deniselle MC, Gonzalez SL, Ibanez C, Labombarda F, Coirini H, Baulieu EE, De Nicola AF. Local synthesis and dual actions of

progesterone in the nervous system: neuroprotection and myelination. *Growth Horm IGF Res.* 2004 Jun;14 Suppl A:S18-33.

*This paper reviews of the effects of progesterone as an autocrine/paracrine hormone in the brain. The brain, spinal cord and peripheral nerves all synthesize progesterone from the precursor, pregnenolone. Macroglial cells, including astrocytes, oligodendroglial cells and Schwann cells, also have the capacity to synthesize progesterone. This production is regulated by cellular interactions. Recent research has suggested the role progesterone plays in the brain is likely a significant one, supporting the viability of neurons and the formation of myelin sheaths. In mice and rat studies, progesterone also demonstrated a neuroprotective effect. These actions of progesterone suggest viable therapeutic possibilities for the prevention and treatment of neurodegenerative diseases, as well as for repair processes and for preserving cognitive functions with age.*

### **Research on Bioidentical Progesterone and the Uterus:**

- Anasti JN, Leonetti HB, Wilson KJ. Topical progesterone cream has antiproliferative effect on estrogen-stimulated endometrium. *Obstet & Gynecol* 2001; 97(4 Suppl.):10S and *Fertil Steril* 2003;79(1):221-2.

*This randomized, controlled study involving 58 postmenopausal women demonstrated that topically applied progesterone cream (Pro-Gest®) had an antiproliferative effect in postmenopausal women who had been given oral estrogens x 14 days prior to progesterone treatment. Treatment with topical progesterone did not differ in effects from vaginally applied progesterone (Crinone®), and both progesterone applications demonstrated a significant effect over placebo. Patients preferred the topical application of progesterone cream.*

- Casanas-Roux F, Nisolle M, Marbaix E, et al. Morphometric, immunohistological and three-dimensional evaluation of the endometrium of menopausal women treated by oestrogen and Crinone ® , a new slow-release vaginal progesterone. *Human Reprod* 1996;11:357-63.

*Twenty estrogen-deprived women were given oral estrogen for 12 days followed by oral estrogen-vaginal progesterone gel for 12 days. Endometrial evaluation occurred before treatment, after the estrogen-only phase and after estrogen-progesterone gel treatment. Atrophy was present before treatment in all patients. Typical proliferative changes occurred after estrogen-only treatment, and secretory transformation occurred after estrogen-progesterone treatment, indicating that sustained-release progesterone gel can effectively counteract the proliferative effects of estrogen treatment in postmenopausal women.*

- Cicinelli E, de Ziegler D, Galantino P, Pinto V, Barba B, Morgese S, Schonauer S. Twice-weekly transdermal estradiol and vaginal progesterone as continuous combined hormone replacement therapy in postmenopausal women: a 1-year prospective study. *Am J Obstet Gynecol* 2002 Sep;187(3):556-60.

*In this study of 35 postmenopausal women, twice-weekly administration of a progesterone vaginal gel (45 mg P4/day) sufficiently protected the endometrium in women receiving transdermal estradiol (0.05 mg/d) as revealed by endometrial thickness and histology. The authors present vaginally applied progesterone as a viable option for hormone replacement therapy at menopause.*

- Dai D, Wolf DM, Litman ES, White MJ, Leslie KK. Progesterone inhibits human endometrial cancer cell growth and invasiveness: down-regulation of cellular adhesion molecules through progesterone B receptors. *Cancer Res* 2002 Feb;62(3):881-6.

*This in vitro study demonstrated that progesterone acts through progesterone receptor B to inhibit endometrial cancer cell invasiveness via the down-regulation of adhesion molecules.*

- Fanchin R, De Ziegler D, Bergeron C, et al. Transvaginal administration of progesterone. *Obstet Gynecol* 1997;90:396-401.

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*Three different doses of transvaginal progesterone gel were administered to 40 estrogen-deprived women aged 25-41 years. Estradiol was administered orally for 28 days, with progesterone added vaginally on alternate days from days 15-27. Plasma gonadotropins, E1, E2 and progesterone were measured, and an endometrial biopsy was obtained to assess endometrial status and estrogen and progesterone receptor determinations. Transvaginal progesterone induced normal secretory transformation despite low serum progesterone levels, suggesting a direct transit of progesterone into the uterus, or "first uterine pass effect."*

- Hodges LC, Houston KD, Hunter DS, Fuchs-Young R, Zhang Z, Wineker RC, Walker CL. Transdominant suppression of estrogen receptor signaling by progesterone receptor ligands in uterine leiomyoma cells. *Mol Cell Endocrinol* 2002 Oct 31;196(1-2):11-20.

*Although estrogen is known to stimulate the growth of uterine fibroids, the effect of progesterone is unclear. The role of progesterone in the development of uterine fibroids (leiomyoma) is examined in this study in an in vivo/in vitro mouse model. Progestins and antiprogestins were utilized to investigate progesterone receptor (PR) signaling in a leiomyoma cell line. Both progestins and antiprogestins inhibited estrogen-mediated growth. PR ligands were also shown to suppress estrogen receptor signaling and leiomyoma cell growth.*

- Leonetti HB, Anasti JN, Landes J. Topical progesterone cream: an alternative progestin in hormone replacement therapy. *Obstet & Gynecol* 2003; 101(4 Suppl.):85.

*20 women completed a 1 year randomized, controlled, cross-over study comparing conjugated equine estrogen (Premarin® , 0.625 mg) paired with progesterone cream (Pro-Gest ® , 20 mg) vs. conjugated equine estrogen paired with medroxyprogesterone acetate (Prempro ® ). Endometrial biopsies were performed at the end of each 6-month arm of the study. No hyperplasia was found in either group. Incidence of spotting was similar in both groups. Participants preferred the progesterone cream composition (76% vs 5%,  $p < 0.001$ ).*

- Montz FJ, Bristow RE, Bovicelli A, Tomacruz R, Kurman RJ. Intrauterine progesterone treatment of early endometrial cancer. *Am J Obstet Gynecol* 2002 Apr;186(4):651-7.

*This study evaluated the use of a progestin-releasing IUD as a feasible treatment for early stage endometrial cancer (IA, grade 1). Twelve subjects were followed for 36 months. Results suggested IUD progestin appeared to resolve some cases of early endometrial cancer.*

- Moyer DL, de Lignieres B, Driguez P, Pez JP. Prevention of endometrial hyperplasia by progesterone during long-term estradiol replacement: influence of bleeding pattern and secretory changes. *Fertil Steril* 1993 May;59(5):992-7.

*It is often presumed that progesterone levels must be high enough to induce endometrial bleeding by withdrawal in order to convey protection during estrogen replacement therapy. In this expanded observational study, the authors sought to determine the influence of withdrawal bleedings, secretory transformation, and reduction of mitosis on the prevention of endometrial hyperplasia during long-term estrogen-replacement therapy. Hysteroscopy and endometrial biopsies were utilized to establish maturation patterns, glandular epithelial mitosis rates, and macroscopic endometrial appearance. The results showed an increase in withdrawal bleeding with higher levels of progesterone, with those levels producing distinct secretory responses. However, incidence of endometrial hyperplasia after 5 yrs of E2/P therapy was independent of secretory changes and withdrawal bleeding, and was more related to the control of mitosis, which was seen even with low doses of progesterone. The authors conclude that a relatively low dose of P may be offered to women seeking hormone replacement therapy with similar levels of endometrial safety.*

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- Stanczyk FZ, Paulson RJ, Roy S. Percutaneous administration of progesterone: blood levels and endometrial protection. *Menopause* 2005;12(2) 232-237.

*This article discusses the controversy about the use of topical progesterone cream and the assumption that serum progesterone levels achieved with progesterone creams are too low to have a secretory effect on the endometrium. Antiproliferative effects on the endometrium have been demonstrated with progesterone creams when circulating levels of progesterone are low. The article claims that effects of topical progesterone creams on the endometrium should not be based on serum progesterone levels, but on histologic examination of the endometrium. Despite the low serum progesterone levels achieved with the creams, salivary progesterone levels are very high, indicating that progesterone levels in serum do not necessarily reflect those in tissues. The mechanism by which the serum progesterone levels remain low is not known. However, one explanation is that after absorption through the skin, the lipophilic ingredients of creams, including progesterone, may have a preference for saturating the fatty layer below the dermis. Because there appears to be rapid uptake and release of steroids by red blood cells passing through capillaries, these cells may play an important role in transporting progesterone to salivary glands and other tissues. In contrast to progesterone creams, progesterone gels are water-soluble and appear to enter the microcirculation rapidly, thus giving rise to elevated serum progesterone levels with progesterone doses comparable to those used in creams.*

- Sager G, Orbo A, Jaeger R, Engstrom C. Non-genomic effects of progestins-inhibition of cell growth and increased intracellular levels of cyclic nucleotides. *J Steroid Biochem Mol Biol* 2003 Jan;84(1):1-8.

*The anti-proliferative effects of three different progestins were compared using 3 human uterine cervix cell lines. In one cell line (C-41) devoid of progesterone receptors (PR) all progestogens studied inhibited growth in the following potency - progesterone (56%) > medroxyprogesterone (38%) > megestrol acetate (25%). Sensitivity demonstrated the same order, with progesterone being the most sensitive to inhibiting growth. This suggests there is a non-genomic action of progestogens that is anti-proliferative. The progestins studied also had anti-proliferative effects on the cell lines exhibiting PR.*

- Whitehead MI, Fraser D, Schenkel L, et al. Transdermal administration of oestrogen/progestogen hormone replacement therapy. *The Lancet* 1990; 335:310-2.

*Sixteen estrogen-deficient women were evaluated on a course of transdermal estradiol and transdermal progestogen for five cycles. Regular withdrawal bleeding was noted in all but one patient. Fourteen endometrial biopsies were performed after the fifth cycle, with no evidence of endometrial hyperplasia.*

#### **Research on the Difference in Effects between Bioidentical Progesterone and Progestins:**

- Bagis T, Gokcel A, Zeyneloglu HB, Tarim E, Kilicdag EB, Haydardedeoglu B. The effects of short-term medroxyprogesterone acetate and micronized progesterone on glucose metabolism and lipid profiles in patients with polycystic ovary syndrome: a prospective randomized study. *J Clin Endocrinol Metab* 2002 Oct;87(10):4536-40.

*This randomized prospective study evaluated and compared the effects of ten days treatment with oral and vaginal progesterone (MP) and medroxyprogesterone acetate (MPA) on glucose metabolism, lipid profiles, and hormonal parameters in 28 patients with polycystic ovary syndrome (PCOS). Oral MPA and oral MP decreased LH ( $P = 0.028$ ,  $P = 0.009$ , respectively) and total testosterone ( $P = 0.013$ ,  $P = 0.037$ , respectively) levels. There was no change in hormonal parameters with vaginal MP. Basal insulin decreased ( $P = 0.021$ ) and insulin sensitivity increased significantly in the oral MPA group. Low density lipoprotein cholesterol (LDL) and lipoprotein (a) levels decreased only in the MPA group. This study concluded that MPA and oral MP may reduce insulin sensitivity in patients with PCOS. Vaginal MP had no effect on glucose metabolism and lipid profiles.*

- Dalton K. The effects of progesterone and progestogens on the foetus. *Neuropharmacology* 1981; 20:1267-9.

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*This article looks at the differing effects of progesterone and synthetic progestogens on the fetus. Of note in this article is evidence that progesterone supplementation may reduce episodes of pre-eclampsia. Synthetic progestogen supplementation during pregnancy may produce a variety of side effects. Several references are made to articles documenting cases of masculinization of external genitalia in female babies. There are two known cases of true hermaphroditism and several cases of behavioral problems developing in adolescent girls whose mothers took oral synthetic progestogens during pregnancy. More problematic may be administration of oral estrogen-progestogen preparations. Side effects may include spina bifida, esophageal anomalies, heart defects and limb reduction deformities.*

- De Lignieres B. Effects of progestogens on the postmenopausal breast. *Climacteric* 2002; 5(3):229-35.

*In this review, the author highlights the differences between progesterone and synthetic progestins in the breast and cautions that progestogens not be "all put in the same bag" with respect to safety. A strong case is made for the protective effect of progesterone on the breast.*

- De Lignieres B. Oral micronized progesterone. *Clin Ther* 1999; 21(1):41-60.

*This review article examines the rationale for selecting oral micronized progesterone over synthetic progestins. It reviews research regarding efficacy and safety and concludes that oral micronized progesterone has fewer side effects than synthetic progestins and is a convenient way to deliver natural progesterone.*

- Fitzpatrick LA, Pace C, Wiita B. Comparison of regimens containing oral micronized progesterone or medroxyprogesterone acetate on quality of life in postmenopausal women: a cross-sectional survey. *J Women Health Gen Based Med* 2000 May;9(4):381-7.

*A cross-sectional survey was conducted to examine quality of life (QOL) related to physiological, somatic, and vasomotor effects of switching progestogen treatment from medroxyprogesterone acetate (MPA) to micronized progesterone in postmenopausal women already using hormone replacement therapy (HRT). One hundred seventy-six women who were currently using hormone replacement therapy (HRT) containing micronized progesterone for 1-6 months and had previously received HRT containing MPA were surveyed to assess QOL. Women using micronized progesterone-containing HRT experienced significant improvement in vasomotor symptoms, anxiety, somatic complaints and depressive symptoms. Women reported improved control of menopausal symptoms and perceptions of their vaginal bleeding patterns while on the micronized progesterone-containing regimen. Approximately 80% of women reported satisfaction with the progesterone-containing therapy. A micronized progesterone-containing HRT therapy offers the potential for improved QOL with respect to menopausal symptoms.*

- Fournier A, et al. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N. *Breast Cancer Res Treat.* 2008;107:103-111.
- Greendale GA, Reboussin BA, Slone S, Wasilauskas C, Pike MC, Ursin G. Postmenopausal hormone therapy and change in mammographic density. *J Natl Cancer Inst* 2003 Jan 1;95(1):30-7.

*Breast cancer risk independently increases with mammographic density. Use of hormone replacement therapy (HRT) postmenopausally is associated with an increase in mammographic density, but the extent of the density increase is unknown. This study evaluated mammograms from 571 of the 875 women enrolled in the PEPI trial at baseline and after 12 months HRT. The women had been randomized to receive placebo, conjugated equine estrogens (CEE) + medroxyprogesterone acetate (MPA) in a continuous or cyclic fashion, or CEE + micronized progesterone (MP). Mammograms were analyzed digitally and a linear regression analysis was utilized to quantify breast density change in all four treatment arms. The adjusted absolute mean changes in mammographic percent density over 12*

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months were 4.76% (95% confidence interval [CI] = 3.29% to 6.23%), 4.58% (95% CI = 3.19% to 5.97%), and 3.08% (95% CI = 1.65% to 4.51%) for women in the CEE+MPA-cyclic, CEE+MPA-continuous, and CEE-MP groups, respectively. Each of those absolute mean changes was statistically significantly different from the adjusted absolute mean change in mammographic percent density for women in the placebo group, which was -0.07% (95% CI = -1.50% to 1.38%). Greater mammographic density was associated with the use of estrogen/progestin combination therapy, although the micronized progesterone containing arm appeared to induce less of an increase than that with MPA.

- Lobo RA. Progestogen metabolism. *J Reprod Med* 1999 Feb;44(2 Suppl):148-52.

*This review clearly elucidates what's known about the differences in metabolism of various progestins as compared with endogenous or natural progesterone. Not only are there different pathways for metabolism, but the route of administration also has a significant effect. The physiologic and pathologic state of the patient further influences the metabolism, and there are measurable variations between patients. The authors also review the differences expressed by various tissues in metabolizing progestogens as well as the different biologic potencies of the various progestogens. Most importantly, the authors state the lack of knowledge about the synthetic progestins as compared to natural progesterone, which has a much better understood effect in the body.*

- Martorano JT, Ahlgrimm M, Meyers D. Differentiating between natural progesterone and synthetic progestogens: clinical implications for PMS management. *Comprehensive Therapy* 1993; 19(3):96-8.

*Clinical observations demonstrate that patients suffering from PMS respond to treatment with natural progesterone, whereas synthetic progestins may exacerbate the condition. The authors review the differences between natural progesterone and synthetic progestins.*

- Miyagawa K, Rosch J, Stanczyk F, and Hermsmeyer K. Medroxyprogesterone interferes with ovarian steroid protection against coronary vasospasm. *Nature Medicine* 1997;3(3): 324-327.

*Ovariectomized rhesus monkeys were treated with physiological levels of 17-beta estradiol in combination with either medroxyprogesterone or progesterone (oral micronized) for four weeks. Following pathophysiological stimulation without injury to induce coronary vasospasm, it was shown that progesterone plus estradiol was protective against vasospasm, whereas estradiol plus medroxyprogesterone allowed vasospasm, concluding that medroxyprogesterone increases risk of coronary vasospasm, while progesterone does not.*

- Montplaisir J, Lorrain J, Denesle R, Petit D. Sleep in menopause: differential effects of two forms of hormone replacement therapy. *Menopause* 2001; 8(1):10-16.

*This randomized clinical trial compared the effects of conjugated equine estrogen (CEE) and medroxyprogesterone acetate to CEE and oral micronized progesterone. Twenty-one postmenopausal women were studied in a sleep lab, with results demonstrating an improvement in subjective measures of menopausal symptoms and sleep in both groups. The group receiving natural progesterone had significantly improved sleep efficiency, whereas the medroxyprogesterone acetate group did not, suggesting that the former might better improve sleep in postmenopausal women.*

- Ojasoo T. Multivariate preclinical evaluation of progestins. *Menopause* 1995; 2( 2): 97-107.

*Specificity profiles of numerous progestins were evaluated by multivariate analysis. Twenty steroid hormones, including natural progesterone, were tested for anti-estrogenic activity and for binding to the androgen, progesterone, and glucocorticoid receptors.*

- Otsuki M, Saito H, Xu X, Sumitani S, Kouhara H, Kishimoto T, Kasayama S. Progesterone, but not medroxyprogesterone, inhibits vascular cell adhesion molecule-1 expression in human vascular endothelial cells. *Arterioscler Thromb Vasc Biol* 2001 Feb;21(2):243-8.

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*This study utilizing human umbilical vein endothelial cells (HUVEC's) demonstrated that progesterone, but not medroxyprogesterone acetate (MPA) inhibited expression of vascular cell adhesion molecule-1 (VCAM-1), demonstrating a role for progesterone in the prevention of atherosclerosis. The differing effects of progesterone and MPA are clinically important, as MPA is widely used in hormone replacement therapy, when, as this research suggests, progesterone might be a more appropriate option.*

- Ottosson UB, Johansson BG, et al. Subfractions of high-density lipoprotein cholesterol during estrogen replacement therapy: A comparison between progestogens and natural progesterone. *Am J Obstetrics and Gynecol* 1993 Mar;151(6): 746-50.

*Fifty-eight postmenopausal women were followed with respect to subfractions of high-density lipoprotein during 3 cycles of unopposed estrogen. The women received either levonorgestrel, medroxyprogesterone acetate, or natural progesterone during the last ten days of the treatment period. Both progestogens significantly lowered HDL cholesterol, whereas natural progesterone had no effect on HDL levels.*

- Osano GM, Webb CM, Chierchia S, Morgani GL, Gabraele M, Sarrel PM, de Ziegler D, Collins P. Natural progesterone, but not medroxyprogesterone acetate, enhances the beneficial effect of estrogen on exercise-induced myocardial ischemia in postmenopausal women. *J Am Coll Cardiol* 2000 Dec;36(7):2154-9

*Eighteen postmenopausal women were randomized to receive 17-beta estradiol with a synthetic progestin (medroxyprogesterone acetate) or a progesterone vaginal gel for 4 weeks, then crossed over to the alternate treatment. Researchers found through treadmill testing that estrogen plus progesterone significantly increased exercise time before myocardial ischemia, when compared to estradiol plus synthetic progestin. In addition, 2 patients on the synthetic progestin arm had to discontinue due to unstable angina. This research suggests that women at risk for cardiovascular disease need to consider progesterone as a safer alternative to synthetic progestins as a part of their hormone replacement therapy regime.*

- Ryan N, Rosner A. Quality of life (QOL) and costs associated with micronized progesterone and medroxyprogesterone acetate in hormone replacement therapy for non-hysterectomized, postmenopausal women. *Clin Ther* 2001 Jul;23(7):1099-115.

*This prospective, multicenter, randomized, parallel-group study enrolled 182 postmenopausal women 45 to 65 years of age and evaluated the quality of life and menopausal symptoms associated with the use of medroxyprogesterone acetate vs oral micronized progesterone when used as a part of a regular hormone replacement therapy. Menopausal symptoms improved in both groups from baseline to 9 months, as did QOL measures. In addition, patients using micronized progesterone had specific improvements in the areas of cognition and menstrual problems whereas the patients using MPA did not. Micronized progesterone was seen as an effective, cost-comparable alternative to MPA as well as being better tolerated.*

- Saarikoski S, Yliskoski M, Penttila I. Sequential use of norethisterone and natural progesterone in premenopausal bleeding disorders. *Maturitas* 1990 Jun;12(2):89-97.

*This randomized controlled study evaluated the effects of norethisterone (NET) and micronized progesterone (MP) on bleeding disorders in pre-menopausal women. 80 patients were randomized to the trial and all were found via endometrial morphology to need progestogen therapy. They were subsequently treated with NET or MP. In both treatment groups, hyperplastic changes disappeared during the first three cycles, with the duration of treatment being 6 months. NET decreased follicle-stimulating hormone, luteinizing hormone, estradiol and sex-hormone-binding globulin levels ( $P < 0.001$ ) whereas no changes were seen during MP treatment. High-density-lipoprotein cholesterol and triglyceride levels were also lowered by NET ( $P < 0.001-0.02$ ) slightly decreased phospholipids. MP*

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*treatment had no effect on lipid profiles suggesting it may be a preferred progestogen for the treatment of bleeding disorders.*

- Sager G, Orbo A, Jaeger R, Engstrom C. Non-genomic effects of progestins-inhibition of cell growth and increased intracellular levels of cyclic nucleotides. *J Steroid Biochem Mol Biol* 2003 Jan;84(1):1-8.

*The anti-proliferative effects of three different progestins were compared using 3 human uterine cervix cell lines. In one cell line (C-41) devoid of progesterone receptors (PR) all progestogens studied inhibited growth in the following potency - progesterone (56%) > medroxyprogesterone (38%) > megestrol acetate (25%). Sensitivity demonstrated the same order, with progesterone being the most sensitive to inhibiting growth. This suggests there is a non-genomic action of progestogens that is anti-proliferative. The progestins studied also had anti-proliferative effects on the cell lines exhibiting PR.*

- Sitruk-Ware R. Progestins and cardiovascular risk markers. *Steroids* 2000 Oct-Nov;65(10-11):651-8.

*This article reviews the effects of various synthetic progestins and progesterone on cardiovascular health. Many synthetic progestins, especially 19-nortestosterone and some 17-hydroxyprogesterones, have negative effects on cardiovascular risk factors, whereas natural progesterone does not. Further studies utilizing natural and other steroids should be considered. Sitruk-Ware R. Progestogens in hormonal replacement therapy: new molecules, risks, and benefits. *Menopause* 2002;9(1):6-15. The classifications of various progestogens (natural and synthetic) are reviewed in terms of their risks and benefits. This review clearly elucidates the differences in the mode of action of various synthetic progestins as well as progesterone.*

#### **Research on Bioidentical Androgens (DHEA and Testosterone) in Women:**

- Anderson CHM, Raju KS, Forling ML, Wheeler MJ. The effects of surgical menopause and parenteral hormone replacement therapy on bone density, menopausal symptoms, and hormone profiles. Department of Gynaecology, St. Thomas Hospital, London, UK.

*45 women undergoing complete hysterectomies were randomized to receive 50-mg estradiol implants, 50 mcg estradiol patches, or 50 mg estradiol and 100 mg testosterone implants. After one year, there was a significant decrease in bone density in the patch group; no decrease in bone density in the pellet implant groups.*

- Arlt W, Justl H, Callies F, et al. Oral dehydroepiandrosterone for adrenal androgen replacement: pharmacokinetics and peripheral conversion to androgens and estrogens in young healthy females after dexamethasone suppression. *J Clin Endocrinol Metab* 1998; 83: 1928-1934.
- Arlt W, Callies F, van Vlijmen JC, Koehler I, Reincke M, Bidlingmaier M, Huebler D, Oettel M, Ernst M, Schulte HM, Allolio B. Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med* 1999 Sep 30;341(14):1013-20.

*In this double-blind study, 24 women with adrenal insufficiency received 50 mg of DHEA. Results showed that DHEA raised the initially low serum levels of DHEA, DHEA-S, and testosterone into the normal ranges; serum concentrations of sex hormone-binding globulin, total cholesterol, and HDL cholesterol decreased significantly. DHEA significantly improved overall well-being as well as scores for depression and anxiety. As compared with placebo, DHEA significantly increased the frequency of sexual thoughts, interest, and satisfaction.*

- Barlow DH, Abdalla HI, Roberts DG, et al. Long-term hormone implant therapy - hormonal and clinical effects. *Obstet Gynecol* 1986; 67:321.

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*75 women were given estradiol or estradiol plus testosterone implants. Bone density was maintained in both groups and both groups had effective menopausal symptom improvement.*

- Burger HG, Hailes J, Menelaus M, et al. The management of persistent menopausal symptoms with oestradiol-testosterone implants: clinical, lipid, and hormonal results. *Maturitas* 1984;6:351-58.
- Casson PR et al. Oral dehydroepiandrosterone in physiologic doses modulates immune function in postmenopausal women. *Am J Obstet Gynecol* 1993 Dec;169(6):1536-9.

*This prospective, randomized, double-blind, crossover study of 11 subjects evaluated the immune impact of oral DHEA in postmenopausal women. The control group showed marked increase in natural killer cell activity and suppressed increased IL-6 production seen in the placebo group (IL-6 in vitro has been shown to be an important bone resorber). Authors concluded DHEA may have immune modulatory functions in older postmenopausal women and may additionally have an antioncogenic effect.*

- Cardozo L, Gibb D, Tuck S, et al. The effects of subcutaneous hormone implants during the climacteric. *Maturitas* 1984;5:177-184.

*This study included 120 women with a total of 469 hormonal implants of 50-mg estradiol and 100-mg testosterone implants over four years. Patients with a uterus were given an oral progestogen. Hot flushes were improved in 100%; depression in 99%; and loss of libido in 92%.*

- Cauley JA, Lucas FL, Kuller LH, Stone K, Browner W, Cummings SR. Elevated serum estradiol and testosterone concentrations are associated with a high risk for breast cancer. Study of Osteoporotic Fractures Research Group. *Ann Intern Med* 1999 Feb 16;130(4 Pt 1):270-7.
- Chu M, Lobo R. Formulations and use of androgens in women. *Mayo Clinic Proc* April 2004(79)Suppl.
- Davis SR, et al. Efficacy and safety of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women: a randomized, placebo-controlled trial. *Menopause* 2006; May-Jun;13(3):387-96.

*This study was a 24-week, randomized, double-blind, placebo controlled trial investigating the safety and effectiveness of a testosterone patch in surgically menopausal women receiving concurrent transdermal estrogen. Women were randomly allocated to placebo (n = 40) or testosterone 300 microg/day (n = 37) treatment. Results indicated that the testosterone-treated group had greater sexual desire score compared with. The domain scores for arousal, orgasm, decreased sexual concerns, responsiveness, and self-image as well as decreased distress were also significantly greater with testosterone therapy than placebo. The frequency of satisfactory sexual events increased but was not statistically different between treatment groups. Adverse events occurred with similar frequency in both groups, and no serious risks of therapy were observed.*

- Davis S, Goldstat R, Papalia M, et al. Effects of aromatase inhibition on sexual function and well-being in postmenopausal women treated with testosterone: a randomized, placebo-controlled trial. *Menopause* 2006;13(1):37-45.
- Davis SR. The therapeutic use of androgens in women. *J Steroid Biochem Mol Biol.* 1999 Apr-Jun;69(1-6):177-84.
- Davis S, Burger H. Androgens and the postmenopausal woman. *J Clin Endocrinol Metab* 1996;81(8):2759-2763.

*This paper is an excellent review of androgens in postmenopausal women. It discusses the role of androgens in women, and the decline of ovarian and adrenal androgens and pre-androgens that can*

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*precede menopause by a decade. It also discusses the potential significant impact this decline can have on women's health. The authors conclude that side effects for androgen replacement (including testosterone subcutaneous implants) in symptomatic women are rare if patients are properly monitored.*

- Davis S, McCloud P, Strauss B, et al. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. *Maturitas* 1995;227-236.

*This prospective, 2 year, single-blind, randomized trial evaluated bone mineral density (BMD) in 34 postmenopausal women who received either 50-mg estradiol pellets, or 50-mg estradiol and 50-mg testosterone pellets. Combined treatment was more effective at improving BMD, as well as improving libido.*

- DeSouza MJ, Slade K, et al. Sublingual administration of micronized Estradiol and progesterone, with and without micronized testosterone: effect on biochemical markers of bone metabolism and bone mineral density. *Menopause* 2000;7(5):318-326.
- Dimitrakakis C, Jones R, Liu A, et al. Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. *Menopause* 2004; 11(5):531-5.

*This study looked at breast cancer incidence in 508 women using bioidentical testosterone implanted pellets alone, or in addition to estrogen/progestin therapy. Women in both groups had lower breast cancer rates than in the "Million Women Study", and women in the testosterone only group had breast cancer rates similar to women who never used HRT. This suggests that testosterone does not increase breast cancer risk, and may even protect against estrogen-induced breast cell proliferation.*

- Gambrell RD, Natrajan PK. Moderate dosage estrogen-androgen therapy improves continuation rates in postmenopausal women: impact of the WHI reports. *Climacteric* 2006;9:224-233.
- Garnett T, Studd J, Watson N, et al. The effects of plasma estradiol levels on increases in vertebral and femoral bone density following therapy with estradiol and estradiol with testosterone implants. *Obstet Gynecol* 1992;79:968-72.
- Garnett T, Studd J, Watson N, et al. A cross-sectional study of the effects of long-term percutaneous hormone replacement therapy on bone density. *Obstet Gynecol* 1991;78:1002-1007.
- Hubayter Z, Simon JA. Testosterone therapy for sexual dysfunction in postmenopausal women. *Climacteric* 20008;11(3):181-91.

*BACKGROUND: After menopause, both surgical and natural, increases occur in the number of women experiencing sexual dysfunction. Although a direct link between sexual dysfunction and endogenous testosterone levels has not been clearly established, testosterone therapy is known to improve the signs and symptoms related to hypoactive sexual desire. However, testosterone supplementation is not approved in the United States for these clinical indications, primarily because of a lack of data evaluating the possible side-effects of these drugs. METHOD: A MEDLINE search was performed, with a priority for well-designed studies (randomized, controlled trials, meta-analysis), for published data related to the efficacy and safety of testosterone therapy in postmenopausal women. RESULTS: Randomized trials have demonstrated an improvement in sexual function with testosterone in postmenopausal women with hypoactive sexual desire disorder, particularly after oophorectomies. Side-effects have been well tolerated and reversible upon discontinuation. CONCLUSION: Exogenous testosterone treatment provides a rational therapeutic alternative to consider in women whose hypoactive sexual desire disorder negatively affects their quality of life and who have no biologic or psychosocial causes not related to decreased androgen levels for their sexual disorder. Women receiving testosterone should be monitored for clinical improvement and for adverse reactions. Transdermal patches and topical gels avoid the hepatic first-pass metabolism and are the preferred*

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*formulations. Testosterone therapy is usually administered concomitantly with estrogen therapy due to a lack of adequate safety and efficacy data on testosterone alone.*

- Kapetanakis E, Dmowski W, Auletta F, et al. Endocrine and clinical effects of estradiol and testosterone pellets used in long-term replacement therapy. *Int J Gynaecol Obstet* 1982;20:387-99.
- Kingsberg SA, Simon JA, Goldstein I. The current outlook for testosterone in the management of hypoactive sexual desire disorder in postmenopausal women. *J Sex Med* 2008; Sep 2;5 Suppl 4:177-8.

*This paper reviews the current state of knowledge about the physiologic effects of testosterone in postmenopausal women, the effects of transdermal testosterone delivery in surgically menopausal women with hypoactive sexual desire disorder (HSDD), and ongoing studies of a transdermal testosterone gel. MAIN OUTCOME MEASURES: Results from the Women's International Study of Health and Sexuality; and studies utilizing the Brief Index of Sexual Functioning for Women, the Psychological General Well-Being Index, and validated instruments that assess female sexual function: the Sexual Activity Log, the Profile of Female Sexual Function, and the Personal Distress Scale. RESULTS: Surgically menopausal women receiving testosterone experience significant increases in total satisfying sexual activity vs. women receiving placebo, significant improvement in all domains of sexual function, and decreases in personal distress, with a favorable safety profile. CONCLUSIONS: Testosterone deficiency may be considered among the underlying causes of HSDD. Currently, testosterone is available to women in the United States only via off-label prescribing or by unregulated compounding of testosterone preparations.*

- Kingsberg S. Testosterone treatment for hypoactive sexual desire disorder in postmenopausal women. *J Sex Med* 2007 Mar;4 Suppl 3:227-34.

*This paper is a review of transdermal (patch) testosterone studies in women. A key feature of these studies was the use of validated study instruments to measure sexual function: Sexual Activity Log (SAL), Profile of Female Sexual Function (PFSF) and Personal Distress Scale. METHODS: The data from the Phase III studies, known as the Investigation of Natural Testosterone in Menopausal women Also Taking Estrogen in Surgically Menopausal women (INTIMATE SM) 1 and 2 were reviewed and the salient information is presented. RESULTS: Both INTIMATE 1 and 2 showed a significant increase in total satisfying sexual activity, via the SAL in those women receiving testosterone, compared with those women in the placebo group. The PFSF instrument demonstrated significant improvements in INTIMATE 1 and 2 in all domains of sexual function in testosterone-treated women compared with the placebo patients. In both studies, personal distress decreased in those patients receiving testosterone, compared with the placebo group. The most commonly reported adverse events were application site reactions. Eight-five percent of patients said they would probably or definitely continue treatment. Conclusions: the transdermal testosterone patch is an effective treatment for hypoactive sexual desire disorder in surgically postmenopausal women receiving concomitant estrogen therapy. The treatment has a favorable safety profile.*

- Lobo RA. Androgens in postmenopausal women: production, possible role, and replacement options. *Obstet Gynecol Surv.* 2001 Jun;56(6):361-76.
- Loeser A. Mammary carcinoma response to implantation of male hormone and progesterone. *The Lancet* 1941:698-700.
- Montgomery J, Brincat M, Tapp A, et al. Effect of oestrogen and testosterone implants on psychological disorders in the climacteric. *The Lancet* 1987:297-299.

*Double-blind, placebo-controlled trial assessing psychological symptoms involving 3 treatment groups of peri and postmenopausal women (N=70): estradiol and testosterone implants, estradiol implant only, or placebo. Depression and anxiety were significantly lower in the pellet treated groups.*

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- Munarriz R, Talakoub L, Flaherty E, et al. Androgen replacement therapy with dehydroepiandrosterone for androgen insufficiency and female sexual dysfunction: androgen and questionnaire results. *J Sex Marital Ther* 2002; 28 (Suppl 1):165-173.
- Miller KK. Androgen deficiency in women. *J Clin Endocrinol Metab* 2001 Jun;86(6):2395-401.
- Notelovitz M. Androgen effects on bone and muscle. *Fertility & Sterility* 2002;77(Suppl 4):S34-41.
- Rako S. Testosterone deficiency: a key factor in the increased cardiovascular risk to women following hysterectomy or with natural aging? *J Womens Health*. 1998 Sep;7(7):825-9.
- Sands R, Studd J, Seed M, et al. The effects of exogenous testosterone on lipid metabolism and insulin resistance in postmenopausal women. *Maturitas* 1997;27(suppl 1):50.
- Savvas M, Studd J, Fogelman I, et al. Skeletal effects of oral oestrogen compared with subcutaneous oestrogen and testosterone in postmenopausal women. *BMJ* 1988;297:331-333.

*Results of this study showed that estradiol implants were more effective at increasing bone density than oral ERT.*

- Schneider HP. Androgens and antiandrogens. *Ann N Y Acad Sci*. 2003 Nov;997:292-306.
- Scott LV, Salahuddin F, Cooney J, Svec F, Dinan TG. Differences in adrenal steroid profile in chronic fatigue syndrome, in depression and in health. *J Affect Disord* 1999 Jul;54(1-2):129-37.
- Secreto G, Zumoff B. Abnormal production of androgens in women with breast cancer. *Anticancer Res* 1994 Sep-Oct;14(5B):2113-7.
- Sherwin B, Gelfand M. Transactions of the fortieth annual meeting of the society of obstetricians gynaecologists of Canada: Differential symptom response to parenteral estrogen and/or androgen administration in the surgical menopause. *Am J Obstet & Gynecol*. 1985 151:153-60.

*In this study, 41 women who underwent complete hysterectomies for benign conditions were randomized to receive estrogen alone, estrogen plus testosterone, or placebo. Women who received combined estrogen-androgen or androgen alone had higher energy levels, sense, or well-being, fewer psychological symptoms, and increased appetite.*

- Simon JA. Safety of estrogen/androgen regimens. *J Reprod Med* 2001 Mar;46(3 Suppl):281-90.
- Somboonporn W et al. Testosterone effects on the breast: implications for testosterone therapy for women. *Endocr Rev*. 2004 Jun;25(3):374-88.
- Somboonporn W, Davis S. Postmenopausal testosterone therapy and breast cancer risk. *Maturitas* 2004;49:267-275.

*This paper evaluated experimental and epidemiological studies pertaining to the role of testosterone in breast cancer. Main outcome measured were mammary epithelial proliferation, apoptosis and breast cancer. Results: In experimental studies, testosterone action is anti-proliferative and pro-apoptotic, and mediated via the AR, despite the potential for testosterone to be aromatized to estrogen. Animal studies suggest that testosterone may serve as a natural, endogenous protector of the breast and limit mitogenic and cancer promoting effects of estrogen on mammary epithelium. In premenopausal women, elevated testosterone is not associated with greater breast cancer risk. The risk of breast*

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*cancer is also not increased in women with polycystic ovary syndrome who have chronic estrogen exposure and androgen excess. However, in postmenopausal women, who are oestrogen deplete and have increased adipose aromatase activity, higher testosterone has been associated with greater breast cancer risk. Conclusion: Available data indicate the inclusion of testosterone in estrogen-progestin regimens has the potential to ameliorate the stimulating effects of hormones on the breast. However, testosterone therapy alone cannot be recommended for estrogen deplete women because of the potential risk of enhanced aromatisation to estrogen in this setting.*

- Stoll BA. Dietary supplements of dehydroepiandrosterone in relation to breast cancer risk. *Eur J Clin Nutr* 1999 Oct;53(10):771-5.
- Tagawa, N, Tamanaka, J, Fujinami, A, Kobayashi, Y, Takaon, T, Fukata, S, Kuma, K, Tada, H, Amino, N. Serum dehydroepiandrosterone, dehydroepiandrosterone sulfate, and pregnenolone sulfate concentrations in patients with hyperthyroidism and hypothyroidism. *Clinical Chemistry* 2000;46(4):523-28.

*In a comparative study of 46 individuals with untreated thyroid disorders to 43 healthy controls, results showed a significant increase in serum DHEA-S but no change in DHEA for those with hyperthyroidism. In hypothyroidism, both DHEA and DHEA-S were significantly decreased. The serum PREG-S was increased in hyperthyroidism and decreased in hypothyroidism. Serum albumin was decreased in hyperthyroidism and serum SHBG was increased in hyperthyroidism.*

- Wiebke, A, Callies, F, Van Vlijmen, J, Koehler, I, Reincke, M, Bidlingmaier, M, Huebler, D, Oettel, M, Ernst, M, Schulte, H, Allolio, B. Dehydroepiandrosterone replacement in women with adrenal insufficiency. *The New England Journal of Medicine* 1999;341(14):1013-19.

*This double-blind crossover study reviewed alternately the effects of 50mg of oral dehydroepiandrosterone (DHEA) daily with placebo in 24 women with adrenal insufficiency. Participants were evaluated using established well-being (depression and anxiety scores) and sexuality (thoughts, interest, satisfaction) scales and serum profiles. Results showed that serum DHEA, DHEA-S and active androgen increased to normal or low-normal levels during treatment. SHBG levels were significantly lower following treatment. IGF-I concentrations increased after treatment (only in women with primary adrenal insufficiency), but IGF-binding protein 3 levels did not change. Serum total and HDL lipoprotein cholesterol levels decreased significantly during treatment. LDL and triglyceride concentrations did not change significantly. Psychological testing scores for well-being and sexuality both improved significantly during treatment. These effects were noticed after treatment for four months, but not after treatment for one month. Authors recommended that treatment with DHEA should be part of hormone replacement therapy for women with adrenal insufficiency.*

- Zeleniuch-Jacquotte A, Bruning PF, Bonfrer JM, Koenig KL, Shore RE, Kim MY, Pasternack BS, Toniolo P. Relation of serum levels of testosterone and dehydroepiandrosterone sulfate to risk of breast cancer in postmenopausal women. *Am J Epidemiol* 1997 Jun 1;145(11):1030-8.
- Zhu YS et al. Natural potent androgens: lessons from human genetic models. *Baillieres Clin Endocrinol Metab.* 1998 Apr;12(1):83-113.

### **Androgen Insufficiency in Women**

- Rivera-Woll LM, Papalia M, Davis SR, et al. Androgen insufficiency in women: diagnostic and therapeutic implications. *Human Reproduction Update* 2004;10(5):421-432.
- Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. *Fertility & Sterility* 2002;77(4): 660-5.

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*Conclusion: A new definition of androgen insufficiency in women has been proposed along with consensus-based guidelines for clinical assessment and diagnosis. A simplified management algorithm for women with low androgen in the presence of clinical symptoms and normal estrogen status has also been proposed.*

- Zumoff B, Strain G, Miller L, et al. Twenty-four-hour mean plasma testosterone concentration declines with age in normal premenopausal women. *J Clin Endocrinol Metab* 1995; 80:1429-1430.

*This study looked at testosterone levels of 33, healthy, non-obese women ages 21 to 51 yrs. Women in their 40s had 50% less testosterone levels than women in their early 20s.*

### **Bioidentical Testosterone Supplementation in Men**

- Amory J, Watts N, Easley K, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab* 2004;89: 503-510.
- Arslanian S, Suprasongsin C. Testosterone treatment in adolescents with delayed puberty: changes in body composition, protein, fat, and glucose metabolism. *J Clin Endocrinol Metab* 1997;82: 3213-3220.
- Glinn S. Testosterone and erectile dysfunction. *J Men's Health Gend* 2004;1(4):407-412.
- Lunenfeld B. Men's Health and Aging: The 5th World Congress on the Aging Male. *The Aging Male* 2006;9(1)1-70.
- Majon M, van der Schouw Y, Thijssen J, et al. Endogenous sex hormones and cardiovascular disease in men. *J of Clin Endocrinol & Metab* 2003;88(11):5076-5086.
- Morales A. Androgen replacement therapy and prostate safety. *European Urology* 2002;41:113-120.
- Okun MS; McDonald WM; DeLong MR. Refractory nonmotor symptoms in male patients with Parkinson disease due to testosterone deficiency: a common unrecognized comorbidity. *Arch Neurol* 2002; 59(5):807-11.
- Okun MS. Beneficial effects of testosterone replacement for the nonmotor symptoms of Parkinson disease. *Arch Neurol* 2002;59(11)1750-3.
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[www.hormonebalance.org/data/Testosterone/Testosterone%20Protocol%20%20www.lef.org.pdf](http://www.hormonebalance.org/data/Testosterone/Testosterone%20Protocol%20%20www.lef.org.pdf)
- Ready RE. Testosterone deficiency and apathy in Parkinson's disease: a pilot study. *J Neurol Neurosurg Psychiatry* 2004;;75(9):1323-6.
- Tan R, Culberson J. An integrative review on current evidence of testosterone replacement therapy for the andropause. *Maturitas* 2003;45: 15-/27.
- Vanderschueren D, Vandenput L, Boonen S, et al. Androgens and bone. *Endocrine Reviews* 2004; 25: 389-425.
- Vermeulen A. Androgen replacement therapy in the aging male—a critical evaluation. *J Clin Endocrinol Metab* 2001;86(6)2380-90.

### **Subcutaneous Hormone Pellets in General**

- Greenblatt R, Suran R. Indications for hormonal pellets in the therapy of endocrine and gynecic disorders. *Am J of Obstet and Gynec* 1949;57:294-301.

### **Research and articles regarding estradiol and testosterone implants in women**

- Anderson CHM, Raju KS, Forling ML, Wheeler MJ. The effects of surgical menopause and parenteral hormone replacement therapy on bone density, menopausal symptoms, and hormone profiles. Department of Gynaecology, St. Thomas Hospital, London, UK, 1997.

*45 women undergoing complete hysterectomies were randomized to receive 50-mg estradiol implants, 50 mcg estradiol patches, or 50 mg estradiol and 100 mg testosterone implants. After one year, there was a significant decrease in bone density in the patch group; no decrease in bone density in the pellet implant groups.*

- Barlow DH, Abdalla HI, Roberts DG, et al. Long-term hormone implant therapy – hormonal and clinical effects. *Obstet Gynecol* 1986; 67:321.

*75 women were given 50mg estradiol (N=36) or 50-mg estradiol plus 100-mg testosterone (N=39) implants every 6 months for 3 years. Both groups had effective menopausal symptom improvement. Estradiol levels in both groups at 3 years were higher than baseline due to accumulation of implanted estradiol. In addition, testosterone levels were higher with each implantation due to accumulation of testosterone. There was no significant weight gain in either treatment group. Liver function and blood pressure did not change in either group. Bone density significantly increased in the ET arm, whereas the E-only arm maintained bone density.*

- Brincat M, Versi E, Moniz CF, et al. Skin collagen changes in postmenopausal women receiving different regimens of estrogen therapy. *Obstet Gynecol* 1987; 70:123.
- Brincat M, Kabalan S, Studd JW, et al. A study of the decrease of skin collagen content, skin thickness, and bone mass in the menopausal woman. *Obstet Gynecol* 1987; 70:840.
- Brincat M, Muscat Baron Y, Galea R. Estrogens and the skin. *Climacteric* 2005; 8:110-123.
- Brincat M, Studd JW, O'Dowd T, et al. Subcutaneous hormone implants for the control of climacteric symptoms. *The Lancet* 1984;16-18.

*55 menopausal women were treated with either 50-mg estradiol and 100-mg testosterone pellets or placebo. All symptoms (hot flushes, heart palpitations, headaches, irritability, lack of concentration, insomnia, depression, dyspareunia, loss of libido, urethral syndrome, and lethargy) improved in the treatment arm; no symptoms improved in the placebo arm. The only symptom that did not improve in either arm was "aches and pains".*

- Buckler HM, Kalsi PK, Cantrill JA, Anderson DC. An audit of oestradiol implants and implant frequency in women undergoing subcutaneous implant therapy. *Maturitas* 1985;22:263.
- Burger HG, Hailes J, Menelaus M, et al. The management of persistent menopausal symptoms with oestradiol-testosterone implants: clinical, lipid, and hormonal results. *Maturitas* 1984;6:351-58.

*17 menopausal women (ages 28 to 50 yrs; mean age 37.5) who complained of low libido and other symptoms despite supplementation with oral estrogens were treated with 40-mg estradiol and 100-mg testosterone implants. Implants were highly effective in nearly all women.*

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- Cardozo L, Gibb D, Tuck S, et al. The effects of subcutaneous hormone implants during the climacteric. *Maturitas* 1984;5:177-184.

*This study included 120 women with a total of 469 hormonal implants of 50-mg estradiol and 100-mg testosterone implants over four years. Patients with a uterus were given an oral progestogen. Hot flushes were improved in 100%; depression in 99%; and loss of libido in 92%.*

- Chu M, Lobo R. Formulations and use of androgens in women. *Mayo Clin Proc* 2004;79 (Supplement).
- Cravioto M, Larrea F, Delgado N, et al. Pharmacokinetics and pharmacodynamics of 25-mg estradiol implants in postmenopausal Mexican women. *Menopause*;8(5):353-360.
- Cronje WH, Vashisht A, Studd JW. Hysterectomy and bilateral oophorectomy for severe premenstrual syndrome. *Human Reproduction* 2004;19(9):2152-2155.
- Davelaar EM, Gerretsen G, Relyveld J. [No increase in the incidence of breast carcinoma with subcutaneous administration of estradiol.] *Ned Tijdschr Geneeskd* 1991;135(14):613-5.

*Between 1972 and mid-1990 the frequency of breast cancer was studied in a group of 261 mostly premenopausal women of the gynaecological department of the Municipal Hospital in The Hague, the Netherlands. All patients had had a total hysterectomy and received estradiol implants. On the basis of a stratified life table giving the cumulative incidence of breast cancer in the Netherlands, an expected incidence of 2 per 1000 person-years was estimated for the observed group (mean observation period: 8.25 years). There were three cases of breast cancer in the observed group. This means an incidence density of 1.4 per 1000 person-years. It is concluded that this form of oestrogen substitution does not increase the risk of breast cancer.*

- Davis S, Walker K, Strauss B. Effects of estradiol with and without testosterone on body composition and relationships with lipids in postmenopausal women. *Menopause* 2000;7(6):395-401.

*33 postmenopausal women were randomized to receive either 50-mg estradiol implants or 50-mg estradiol and 50-mg testosterone every 3 months for 2 years (women with an intact uterus were given cyclic oral progestins). Women were not re-inserted with estradiol or testosterone implants if levels were high at the time of reinsertion. 32 women completed the study (17 in E group; 15 in E&T group). Neither group experienced weight gain, although the E&T group had higher fat free mass at 2 years. Both groups had lower total and LDL cholesterol levels.*

- Davis S. Androgen treatment in women. *MJA* 1999;170:545-9.
- Davis S, Burger H. Androgens and the postmenopausal woman. *J Clin Endocrin Metab* 1996;81(8):2759-2763.

*This paper is an excellent review of androgens in postmenopausal women. It discusses the role of androgens in women, and the decline of ovarian and adrenal androgens and pre-androgens that can precede menopause by a decade. It also discusses the potential significant impact this decline can have on women's health. The authors conclude that side effects for androgen replacement (including testosterone subcutaneous implants) in symptomatic women are rare if patients are properly monitored.*

- Davis S, McCloud P, Strauss B, et al. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. *Maturitas* 1995;227-236.

*This prospective, 2 year, single-blind, randomized trial evaluated bone mineral density (BMD) in 34 postmenopausal women who received either 50-mg estradiol implants, or 50-mg estradiol and 50-mg testosterone implants every 3 months for 2 years. E plus T was more effective at improving BMD and libido than E alone.*

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- Dimitrikakis C, Jones R, Liu A, Bondy L. Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. *Menopause* 2004;11(5):531-5.

*This study looked at 508 patients who received 50 to 150 mg testosterone implants (dosage titrated to relieve symptoms and improve bone density and to minimize adverse effects – mean dosage 100-mg). in addition to usual hormone replacement in Australia. Average age at start of study was 56.4 years, and mean duration of follow-up was 5.8 years. Breast cancer incidence in testosterone users was close to that reported for hormone therapy never-users, suggesting that the addition of testosterone to conventional hormone therapy for postmenopausal women does not increase the risk of breast cancer. Because users of HRT are expected to have an increased risk, testosterone supplementation may reduce hormone therapy-associated breast cancer risk.*

- Dimitrikakis C, Zhou J, Wang J, et al. A physiologic role for testosterone in limiting estrogenic stimulation of the breast. *Menopause*;10(4)292-8.
- Dow M, Hart D, Forrest C. Hormonal treatments of sexual unresponsiveness in postmenopausal women: a comparison study. *Br J of Ob & Gyn* 1983;90:361-6.
- Gambrell RD, Natrajan PK. Moderate dosage estrogen-androgen therapy improves continuation rates in postmenopausal women: impact of the WHI reports. *Climacteric* 2006;9:224-233.

*This paper looked at the continuation rates for hormone replacement in 814 menopausal women. During the 3 years of observation, 85% of women continued HRT. More than 87% of these women used estradiol and testosterone implants; the remaining women used injectables, patches, or oral hormones. Continuation rates for pellet implant users were 96.7% for 10 years and 88.8% for 20 year, suggesting a high degree of satisfaction with pellet implants. Pellet dosages (25 to 75-mg estradiol & 75 to 150-mg testosterone) were The majority of women received pellets every 4 ½ to 6 months.*

- Garnett T, Studd J, Watson N, et al. The effects of plasma estradiol levels on increases in vertebral and femoral bone density following therapy with estradiol and estradiol with testosterone implants. *Obstet Gynecol* 1992;79:968-72.
- Garnett T, Studd J, Watson N, et al. A cross-sectional study of the effects of long-term percutaneous hormone replacement therapy on bone density. *Obstet Gynecol* 1991;78:1002-1007.
- Goel N. Hormone replacement therapy part I: prescribing HRT – recent trends.  
file:///D:/hormone/data/Pellets Hormone Implants/Goel Dose India E 50 25 older T 100.htm (1 of 11)3/11/2006 .
- Holland EF, Leather AT, Studd JW. The effect of 25-mg percutaneous estradiol implants on the bone mass of postmenopausal women. *Obstet Gynecol* 1994;83:43-6.
- Hunter D, Akande E, Carr P, Stallworthy J. The clinical and endocrinological effect of oestradiol implants at the time of hysterectomy and bilateral salpingo-oophorectomy. *Obstet Gynecol* 1973;80:827-833.
- Kapetanakis E, Dmowski W, Auletta F, et al. Endocrine and clinical effects of estradiol and testosterone pellets used in long-term replacement therapy. *Int J Gynaecol Obstet* 1982;20:387-99.
- Khastgir G, Studd JW, Fox SW, et al. A longitudinal study of the effect of subcutaneous estrogen replacement on bone in young women with Turner's syndrome. *J Bone Mineral Res* 2003;(5):925-32.
- Khastgir G, Studd J, Holland N. Anabolic effect of estrogen replacement on bone in postmenopausal women with osteoporosis: histomorphometric evidence in a longitudinal study. *J Clin Endocrinol Metab* 2001;86:289-295.

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- Khastgir G, Studd J. Patient's outlook, experience, and satisfaction with hysterectomy, bilateral oophorectomy, and subsequent continuation of hormone replacement therapy. *Am J Obstet Gynecol* 2000;183(6):1427-33.
- Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. *Climacteric* 2005;8(Suppl 1):3-63.

*This is a comprehensive review of the pharmacokinetics and pharmacodynamics of natural and synthetic estrogens and progestogens used in contraception and HRT. The paper describes the mechanisms of action, the relation between structure and hormonal activity, differences in hormonal pattern and potency, peculiarities in the properties of certain steroids, tissue-specific effects, and the metabolism of the available estrogens and progestogens. The influence of the route of administration on pharmacokinetics, hormonal activity and metabolism is presented, and the effects of oral and transdermal treatment with estrogens on tissues, clinical and serum parameters are compared. The effects of oral, transdermal (patch and gel), intranasal, sublingual, buccal, vaginal, subcutaneous (pellets) and intramuscular administration of estrogens, as well as of oral, vaginal, transdermal, intranasal, buccal, intramuscular and intrauterine application of progestogens are discussed.*

- Lobo R. Androgens in postmenopausal women: production, possible role, and replacement options. *Obstet & Gynecol* 2001;56:361-376.
- Lobo R, March C, Goebelsmann U, et al. Subdermal estradiol pellets following hysterectomy and oophorectomy. *Obstet & Gynecol* 1980;138:714-9.

*This study looked included 22 women (ages 29-50 years) who received 25-mg estradiol pellets after complete hysterectomy. Serum estradiol levels remained steady in the follicular range, HDL cholesterol levels increased, and women remained symptom-free for 5-6 months after insertion. The estradiol to estrone ration remained >1 (as it is in ovulatory, menstruating women), unlike with oral ERT. The authors conclude that "estradiol pellets are an effective form of parenteral ERT and offer both practical and theoretical advantages over forms of ERT."*

- Loeser A. Mammary carcinoma response to implantation of male hormone and progesterone. *The Lancet* 1941:698-700.
- Magos A, Zilkha K, Studd K. Treatment of menstrual migraines by oestradiol implants. *J of Neurology, Neurosurgery, and Psychiatry* 1983;46:1044-46.

*24 women with menstrual migraines were given estradiol pellets for up to 5 years. 23 of the women improved, and 20 (83%) became completely or almost completely headache-free. The results support the theory that estrogen withdrawal in the late luteal phase can precipitate migraines, and that preventing hormonal fluctuations with estradiol implants can prevent them.*

- Mishell D. A clinical study of estrogenic therapy with pellet implantation. *Obstet Gynecol* 1941;41:1009-1017.
- Montgomery J, Brincat M, Tapp A, et al. Effect of oestrogen and testosterone implants on psychological disorders in the climacteric. *The Lancet* 1987:297-299.

*Double-blind, placebo-controlled trial assessing psychological symptoms involving 3 treatment groups of peri and postmenopausal women (N=70): 50-mg estradiol and 100-mg testosterone implants, 50-mg estradiol implant only, or placebo. Depression and anxiety were significantly lower in the implant treated groups.*

- Nagamani M, Lin T, McDonough P, et al. Clinical and endocrine studies in menopausal women after estradiol implantation. *Obstet Gynecol* 1977;50:541-547.

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- Naessen T. Maintained bone density at advanced ages after long term treatment with low dose oestradiol implants. *Br J Obstet Gynecol* 1993;100: 454-459.

*35 women receiving 20-mg estradiol pellets were compared with age-matched controls. Bone densities in the forearm, spine, and hip were 20-25% higher in women with estradiol pellets.*

- Natrajan P, Gambrell D. Estrogen replacement therapy in patients with early breast cancer. *Obstet Gynecol* 2002;187:289-95.

*This study looked at 123 early breast cancer patients. Most patients received estradiol pellets, testosterone pellets, or both. Neither estradiol nor testosterone pellets increased the risk of recurrence or death in these patients.*

- Natrajan P, Soumakis K, Gambrell D. Estrogen replacement therapy in women with previous breast cancer. *Obstet Gynecol* 1999;181:288-295.

*This review discusses how testosterone supplementation (pellet or methyl) plus ERT improves bone density to a greater extent than ERT alone.*

- Nezhat C, Karpas A, Greenblatt R, et al. Estradiol implants for conception control. *Obstet Gynecol* 1980;138:1151-1156.

- Notelovitz M, Johnston M, Smith S, et al. Metabolic and hormonal effects of 25-mg and 50-mg 17 beta-estradiol implants in surgically menopausal women. *Obstet Gynecol* 1987;70:749.

*This study included 12 surgically menopausal women. Results showed that estradiol implants improved bone density without any adverse cardiovascular side effects.*

- Notelovitz M. Androgen effects on bone and muscle. *Fertility & Sterility* 2002;77(Suppl 4):S34-41.

- Oettinger M, Barak S, et al. Subcutaneous implantation of pure crystalline estradiol pellets for conception control. *Gynecol Obstet Invest* 2005;59:119-125.

- Owen E, Siddle N, McGarrigle H, et al. 25-mg oestradiol implants – the dosage of first choice for subcutaneous oestrogen replacement therapy? *Br J Obstet Gynaecol* 1992;99:671-75.

- Panay N, Versi E, Savvas M. A comparison of 25 and 50-mg oestradiol implants in the control of climacteric symptoms following hysterectomy and bilateral salpingo-oophorectomy. *Br J Obstet Gynaecol* 2000;107:1012-1016.

*This double-blind, randomized trial of 44 women showed that 25-mg and 50-mg estradiol pellets were equally effective at controlling menopausal symptoms. There was no difference in duration of effectiveness between the two dosages.*

- Panay N, Zamblera D, Sands R, et al. Low dose 25 mg oestradiol implants and 1 mg norethisterone as continuous combined hormone therapy: a prospective study. *BJOG* 2002;109:958-960.

- Pereda C, Hannon R, Naylor K, et al. The impact of subcutaneous oestradiol implants on biochemical markers of bone turnover and bone mineral density in postmenopausal women. *BJOG* 2002;109:812-820.

- Pirwany I, Sattar N, Greer I, et al. Supraphysiological concentrations of estradiol in menopausal women given repeated implant therapy do not adversely affect lipid profiles. *Human Reproduction* 2002;17:825-829.

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- Purdie DW, Ballard PA, Wahab M, Cooper A. Bone mineral density (BMD) at lumbar spine and femoral neck in hysterectomized women treated with chronic oestradiol implantation.
- Rufford J, Hextall A, Cardozo L, et al. A double-blind placebo-controlled trial on the effects of 25 mg estradiol implants on the urge syndrome in postmenopausal women. *International Urogynecology Journal and Pelvic Floor Dysfunction* 2003;14(2):78-83.
- Sands R, Studd J, Seed M, et al. The effects of exogenous testosterone on lipid metabolism and insulin resistance in postmenopausal women.
- Savvas M, Studd J, Fogelman I, et al. Skeletal effects of oral oestrogen compared with subcutaneous oestrogen and testosterone in postmenopausal women. *BMJ* 1988;297:331-333.

*Results of this study showed that estradiol implants were more effective at increasing bone density than oral ERT.*

- Savvas M, Studd J, Norman S, et al. Increase in bone mass after one year of percutaneous oestradiol and testosterone implants in post-menopausal women who have previously received long-term oral estrogens. *Br J of Ob & Gyn* 1992;99:757-760.
- Seeds M, Sands R, McLaren M, et al. The effect of hormone replacement therapy and route of administration on selected cardiovascular risk factors in postmenopausal women. *Family Practice* 2000;17(6):497-507.
- Servy EJ, Bryner JR, Scholer J. Effects of subcutaneous estradiol implants after oophorectomy. *Advances in Contraceptive Delivery Systems* 1991;2:1-19.
- Somboonporn W, Davis S. Postmenopausal testosterone therapy and breast cancer risk. *Maturitas* 2004;49:267-275.

*This paper evaluated experimental and epidemiological studies pertaining to the role of testosterone in breast cancer. Main outcome measured were mammary epithelial proliferation, apoptosis and breast cancer. Results: In experimental studies, testosterone action is anti-proliferative and pro-apoptotic, and mediated via the AR, despite the potential for testosterone to be aromatized to estrogen. Animal studies suggest that testosterone may serve as a natural, endogenous protector of the breast and limit mitogenic and cancer promoting effects of estrogen on mammary epithelium. In premenopausal women, elevated testosterone is not associated with greater breast cancer risk. The risk of breast cancer is also not increased in women with polycystic ovary syndrome who have chronic estrogen exposure and androgen excess. However, in postmenopausal women, who are oestrogen deplete and have increased adipose aromatase activity, higher testosterone has been associated with greater breast cancer risk. Conclusion: Available data indicate the inclusion of testosterone in estrogen-progestin regimens has the potential to ameliorate the stimulating effects of hormones on the breast. However, testosterone therapy alone cannot be recommended for estrogen deplete women because of the potential risk of enhanced aromatisation to estrogen in this setting.*

- Staland B. Treatment of menopausal oestrogen deficiency symptoms in hysterectomised women by means of 17-B-oestradiol pellet implants. *Acta ObGyn Scand* 1978;57:281-85.

*94 women were treated with subcutaneous estradiol implants (20 mg) for menopausal symptoms (589 implantations total). Women reported very good resolution of symptoms with only 2 patients reporting unsatisfactory results regarding sweating and hot flushes. Many patients had previously used other forms of ERT and nearly all preferred pellet implantation.*

- Stanczyk F. Editorial: parenteral versus oral treatment of postmenopausal women with estrogen. *Menopause* 2007 14(6)968-70.

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- Studd JW. The dose response of per-cutaneous oestradiol implants on the skeletons of postmenopausal women. *Br J ObGyn* 1994;101:787-791.
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- Thom M, Collins WP, Studd JW. Hormonal profiles in postmenopausal women after therapy in subcutaneous implants. *British J of Obstetrics and Gynaecology* 1988;88:426-433.
- Vedi S, Purdie W, Ballard P, et al. Bone remodeling and structure in postmenopausal women treated with long-term, high-dose estrogen therapy. *Osteoporosis Int* 1999;10:52-58.
- Worboys S, Kotsopoulos D, Teede H, et al. Evidence that parenteral testosterone therapy may improve endothelium-dependent and independent vasodilation in postmenopausal women already receiving estrogen. *J Clin Endocrinol Metab* 2001;86:158-61.

### Research and articles regarding testosterone pellet implants in men

- Brady BM, Waltoni M, Hollowi N, et al. Depot testosterone with etonogestrel implants result in induction of azoospermia in all men for long-term contraception. *Human Reproduction* 2004 19(11):2658-2667.
- Cantrill JA, Dewis P, Large DM, et al. Which testosterone replacement therapy? *Clin Endocrinol (Oxf)* 1984; 21:97-107.

*This study compared three different forms of testosterone replacement – intramuscular injection of mixed testosterone esters (250 mg), subcutaneous testosterone pellet implants (6 x 100 mg), and oral testosterone undecanoate (80 mg twice daily). In six men given oral testosterone, serum testosterone levels were markedly variable both between subjects, and within the same subject on different days. This is likely due to variability in absorption of oral testosterone undecanoate. In nine men given injected testosterone, serum testosterone levels rose to supraphysiological peak concentrations 24-48 hours after injection, followed by decline to baseline level after 2-3 weeks. In six men who received testosterone pellet implants, serum testosterone remained within the normal range for 4-5 months. Serum estradiol levels were within normal range in the oral and pellet implant group, but showed a supraphysiological peak 24-48 hours after injection. 5 alpha-dihydrotestosterone (DHT) levels paralleled those of testosterone, with DHT:T ratios highest for oral testosterone. The authors conclude that testosterone implants remain overall the most physiological form of replacement, and that pellets are well accepted with few side effects.*

- Conway A, Boylin L, Howe C, et al. Randomized clinical trial of testosterone replacement therapy in hypogonadal men. *Int J Andrology* 1988;11:247-264.

*15 men were given 3 treatment periods, each separated by a washout period. The treatments included IM injections of testosterone esters every 2 weeks, oral testosterone undecanoate, and subcutaneous testosterone pellets. Pellet implants produced the most prolonged, elevated total and free testosterone levels for up to 4 months. The authors concluded that pellet implants gave the closest approximation to steady-state, physiological delivery of the methods tested.*

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- Dunning T, Ward G. Testosterone replacement therapy – perceptions of participants and partners. *Issues and Innovations in Nursing Practice* 2004;467-74.

*This study evaluated sense of well-being and sexual function in 10 men receiving testosterone pellet implants, 5 with partners and 5 without partners. Decreased testosterone levels had a statistically significantly different effect on libido at time zero between men with and without partners and on ability to sustain an erection, but the ability to achieve an erection persisted over the 6 months in both male groups.*

- Gooren L. New long-acting androgens. *World J Urol* 2003;21:306-10.

*This article acknowledges the major goal of testosterone replacement therapy is to replace testosterone levels at as close to physiological concentrations as is possible. General agreements about such an androgen replacement therapy are (1) a delivery of the physiological amount of testosterone (3-10 mg/d); (2) consistent levels of testosterone, 5 $\alpha$ -dihydrotestosterone (DHT) and 17 $\beta$ -estradiol (E<sub>2</sub>) within normal physiological ranges; (3) a good safety profile without adverse effects on the prostate, serum lipids, liver or respiratory function; and (4) convenience in usage, patient-friendly, with a relative independence of medical services. The article discusses that pellets replicate the daily dosage of testosterone production in eugonadal men, with consistent levels for 4-6 months after implantation.*

- Gooren L, Bunk M. Androgen replacement therapy: present and future. *Drugs* 2004;64(17):1861-1891.
- Hair W, Wu F, Lincoln G. An investigation of the effectiveness of testosterone implants in combination with the prolactin inhibitor quinagolide in the suppression of spermatogenesis in men. *Human Reproduction* 2003;18(4):749-755.
- Handelsman DJ, Mackey MA, Howe C, et al. An analysis of testosterone implants for androgen replacement therapy. *Clin Endocrinol (Oxf)* 1997; 47: 311-6

*Review of 13 years of experience (220 men, 973 implant procedures) using testosterone pellets in order to identify pattern of usage, including continuation rates, and adverse events, including extrusion. Bleeding, infection, and fibrosis were rare; extrusion was related to work or procedure problems. Overall continuation rate with pellets increased with duration of use, 88% after the first implantation, 95% after the third.*

- Handelsman DJ, Conway AJ, Howe CJ, et al. Establishing the minimum effective dose and additive effects of depot progestin in suppression of human spermatogenesis by a testosterone depot. *J Clin Endocrinol Metab* 1996;81:4113-4121.
- Handelsman DJ, Conway AJ, Boylan LM. Suppression of human spermatogenesis by testosterone implants. *J Clin Endocrinol Metab* 1992;175:1326-1332.
- Handelsman DJ, Conway AJ, Boylan LM. Pharmacokinetics and pharmacodynamics of testosterone pellets in man. *J Clin Endocrinol Metab* 1990;71:216-222.

*Pharmacokinetics and pharmacodynamics of subcutaneous testosterone pellets were compared in this prospective, cross-over clinical trial. Plasma, free and total testosterone, SHBG, LH, and FSH were measured before and at monthly intervals for at least 6 months after 111 implantations in 43 men. Total and free testosterone levels were shown to peak at month one, and were maintained for 4-6 months depending on dosage. The authors conclude that testosterone pellets provide "very satisfactory depot androgen replacement exhibiting many desirable features for androgen replacement."*

- Jockenhovel F, Blum W, Vogel E, et al. Testosterone substitution normalizes elevated serum leptin levels in hypogonadal men. *J Clin Endocrinol Metab* 1997;82:2510-2513.

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- Jockenhovel F, Vogel E, Kreutzer M, et al. Pharmacokinetics and pharmacodynamics of subcutaneous testosterone implants in hypogonadal men. *Clin Endocrinol (Oxf)* 1996;45:61-71.

*50 men received testosterone implants for a total of 112 implantations. The only side effect noted was extrusion of pellets in 3 men. When given the choice, all patients except one preferred testosterone pellets to previous testosterone replacement methods. The authors conclude that "testosterone pellets are the androgen formulation with the longest biological action and strongest pharmacodynamic efficacy in terms of gonadotrophin suppression. The pharmacokinetic features are advantageous compared to other testosterone preparations and patient acceptance is high."*

- Kelleher S, Howe C, Conway A, Handelsman. Testosterone release rate and duration of action of testosterone pellet implants. *Clin Endocrinol* 2004;60:420-428.
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*This article was published in 1939 discussing the use of testosterone pellet implants and case studies of two hypogonadal males.*

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- Zacharin M, Pua J, Kanumakala S. Bone mineral density outcomes following long-term treatments with subcutaneous testosterone pellet implants in male hypogonadism. *Clin Endocrinol* 2003;58:691-95.

*37 men with primary or secondary hypogonadism received long-term (mean 6.6 yrs) subcutaneous testosterone pellet implants. Bone density for treated men was the same as age-matched men not needing treatment. The authors conclude that subcutaneous testosterone pellet implants are safe and acceptable to the patient, and result in adequate bone mass and maintenance of normal bone mineral*

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*density. They also surmise that sustained physiological levels of testosterone via pellets may contribute to increased androgen effect at the receptor level.*

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