Research & Articles Regarding Estradiol & 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 50-mg 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. HormoneSynergy® Kathryn Retzler, ND 2705 E. Burnside St., Suite 206 Portland, OR 97214 503.230.7990

- 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.

• 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 oopherectomy 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 hysteroadnexectomy 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 HormoneSynergy® Kathryn Retzler, ND 2705 E. Burnside St., Suite 206 Portland, OR 97214 503.230.7990 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.

• 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 additional 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. HormoneSynergy® Kathryn Retzler, ND 2705 E. Burnside St., Suite 206 Portland, OR 97214 503.230.7990

• 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

dosage ranged from 25 to 75-mg estradiol & 75 to 150-mg testosterone. 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.

• 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. HormoneSynergy® Kathryn Retzler, ND 2705 E. Burnside St., Suite 206 Portland, OR 97214 503.230.7990

• 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 headachefree. 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. HormoneSynergy® Kathryn Retzler, ND 2705 E. Burnside St., Suite 206 Portland, OR 97214 503.230.7990

• 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.

• 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. HormoneSynergy® Kathryn Retzler, ND 2705 E. Burnside St., Suite 206 Portland, OR 97214 503.230.7990

• 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 salpingooophorectomy. 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.

• 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 & Gyn1992;99:757-760. HormoneSynergy® Kathryn Retzler, ND 2705 E. Burnside St., Suite 206 Portland, OR 97214 503.230.7990

• 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 oopherectomy. Advances is Contraceptive Delivery Systems 1991;2:1-19.

- Sherwin BB, GElfand MM. (1985). Differential symptom responses to parenteral estrogen and or androgen administration in the surgical menopause. Am J Obstet Gyncol 151(2): 153-60.

• 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.

• Stanczyk F, Shoupe D, Nunez V, et al. A randomized comparison of non-oral estradiol delivery in postmenopausal women. Am J ObGyn 1988;159:1540-6.

• Studd JW. The dose response of per-cutaneous oestradiol implants on the skeletons of postmenopausal women. Br J ObGyn 1994;101:787-791. HormoneSynergy® Kathryn Retzler, ND 2705 E. Burnside St., Suite 206 Portland, OR 97214 503.230.7990

• Suhonen SP, Sipinen S, Lahteenmaki P, et al. Postmenopausal oestrogen replacement therapy with subcutaneous estradiol implants. Maturitas 1993;16:123-131.

• Suhonen SP, Lahteenmaki P, Rauramo I. Sustained-release estradiol implants in HRT: one year results on hormone levels and menopausal symptoms. Steroid Research Laboratory, Institute of Biomedicine, University of Helsinki 1997.

• 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.

In this study, 33 women received 50-mg testosterone pellets in addition to HRT. 15 women received HRT only. Six weeks after implantation, the treated group had improved endothelium-dependent (flow-mediated) and endothelium-independent (glyceryl trinitrate-mediated) brachial artery vasodilation.