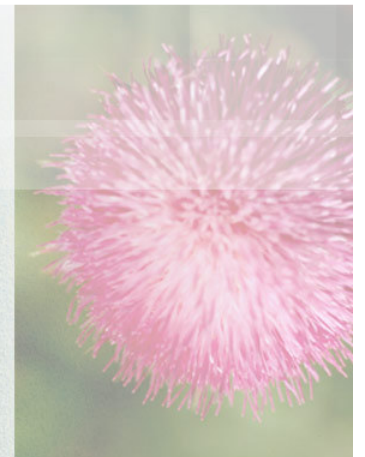
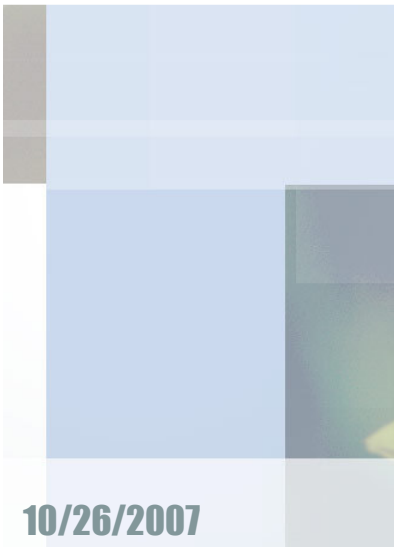
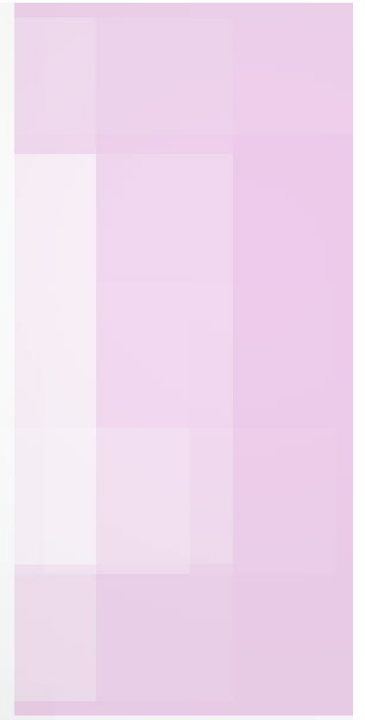




Jace Wellness Center

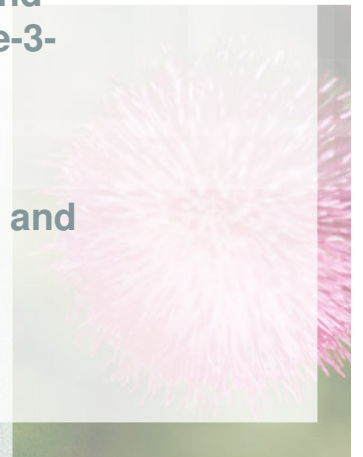
Bio-Identical Hormone Replacement Therapy Is it for you?



Definitions



- **Bio-Identical** isomolecular
- **Micronized** ultra-fine particle size of hormones that allows for increased aqueous dissolution in the GI tract
- **Natural** derived from plant or animal; bio-identical or not bio-identical; also called semi-synthetic
- **Estropipate** not bio-identical; plant-derived; made from purified crystalline estrone; “Ogen” and “Ortho-Est”
- **Esterified Estrogen** not bio-identical; plant-based; made from soy and wild yams; “Estratab” and “Menest”
- **Conjugated Estrogen** not bio-identical; any estrogen bound with another molecule as in estrone-3-sulfate; “Premarin” and “Cenestin”
- **Progestin** not bio-identical; synthetic progesterone; “Provera”
- **Progestogens** term encompassing both progestin and progesterone





Hormone Replacement Therapy

Bio-Identical

Non Bio-Identical

Synthetic

Semi-synthetic
Aka "Natural"

Synthetic

Semi-synthetic
Aka "Natural"

Estrace
Gynediol
Estraderm
Vivelle
Climara
Fempatch
Esclim
Prometrium

Triest
Biest
Estrone
Estradiol
Estriol
Progesterone
DHEA
Testosterone

Provera

Premarin – horse derived
Cenestin – plant derived
Estratab – plant derived
Menest – plant derived
OrthoEst- plant derived

History



Earliest documented use occurred in AD 1025 when the Chinese extracted sex hormones from human urine; the urine was first evaporated and then further heated and chemically processed thereby enabling the salts and urea to be removed, leaving a crystalline substance rich in steroid and protein hormones that the Chinese called *ch'iu shih* ("autumn mineral").

History



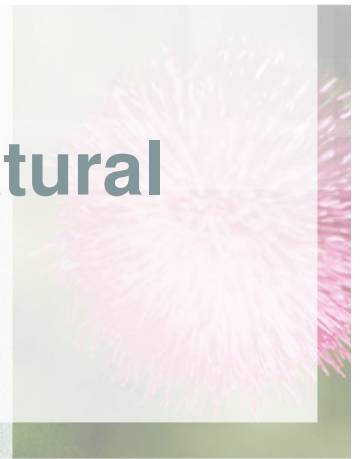
In the late 1920's before doctors learned about tissue rejection, men had surgical implants of testicles or parts of testicles from executed prisoners, monkeys, goats and other animals. The operations remained in vogue until the apparent efficacy of the implants was revealed to be a powerful placebo effect.

Dabbs JM and Dabbs MG; Heroes, Rogues, and Lovers: Testosterone and Behavior

History

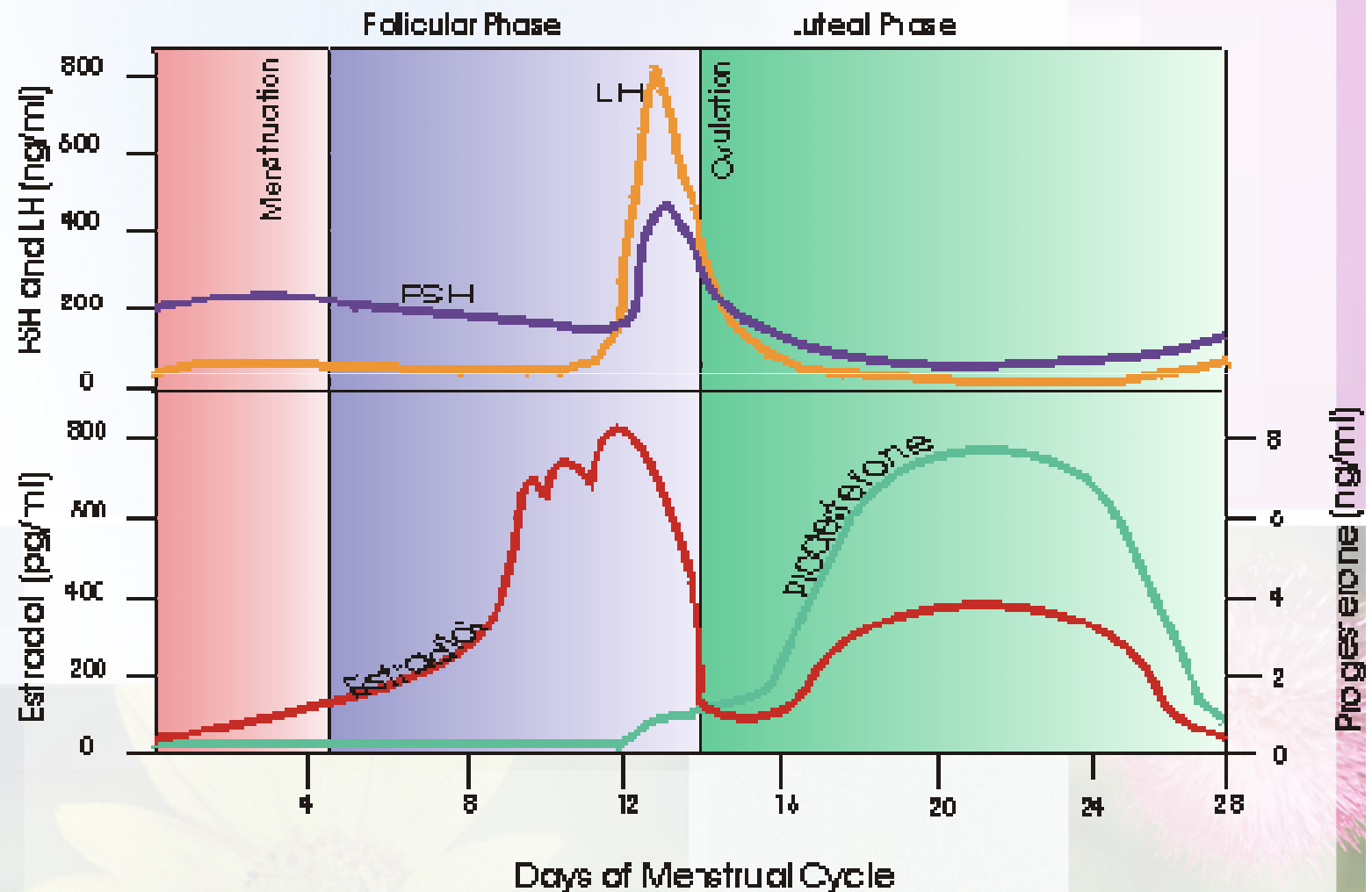


- In the early 1980's, Ed Thorpe, compounding pharmacist at Kripps Pharmacy in Vancouver, BC volunteered to compound Jonathan Wright, MD's combined prescription of estrone, estradiol, and estriol together in identical-to-natural quantities and proportions, now known as "Triest"
- In 1979, John Lee, MD started researching and prescribing natural bio-identical progesterone





Approximate Concentrations of Pituitary and Ovarian Hormones During Menstrual Cycle



Estradiol & Progesterone Fluctuation



Remember, progesterone is measured in nanograms, whereas estradiol is measured in picograms. Hence, there is a lot more progesterone than estradiol production.

1 milligram (mg) = 1000 microgram (ug)

1 microgram (ug) = 1000 nanogram (ng)

1 nanogram (ng) = 1000 picogram (pg)

Also known, but not noted on the graph: the timing of ovarian secretion of androstenedione (precursor to testosterone) resembles that of estradiol; the plasma levels of testosterone stay fairly stable throughout the cycle except for a slight rise before ovulation.

A Different Kind of Menstrual Cycle



Sex Hormones



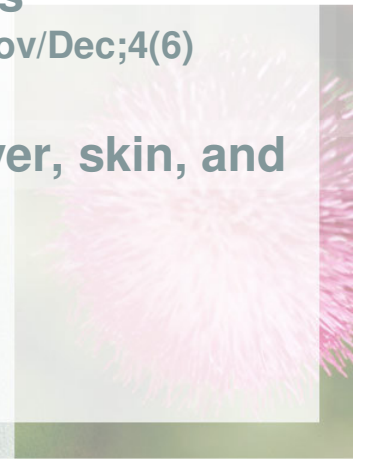
- **Estrone (E1)** – middle strength estrogen; primary estrogen produced after menopause; converted in body fat from androstenedione
- **Estradiol (E2)** – primary estrogen produced before menopause to a total amount of 100-300mcg per day; 10-20pg per day is produced post-menopause from estrone conversion in peripheral tissues; when used at HRT, estradiol is converted in the small bowel to estrone by the gut-associated cytochrome P-450 enzymes

International Journal of Pharmaceutical Compounding, 2000 Nov/Dec;4(6)

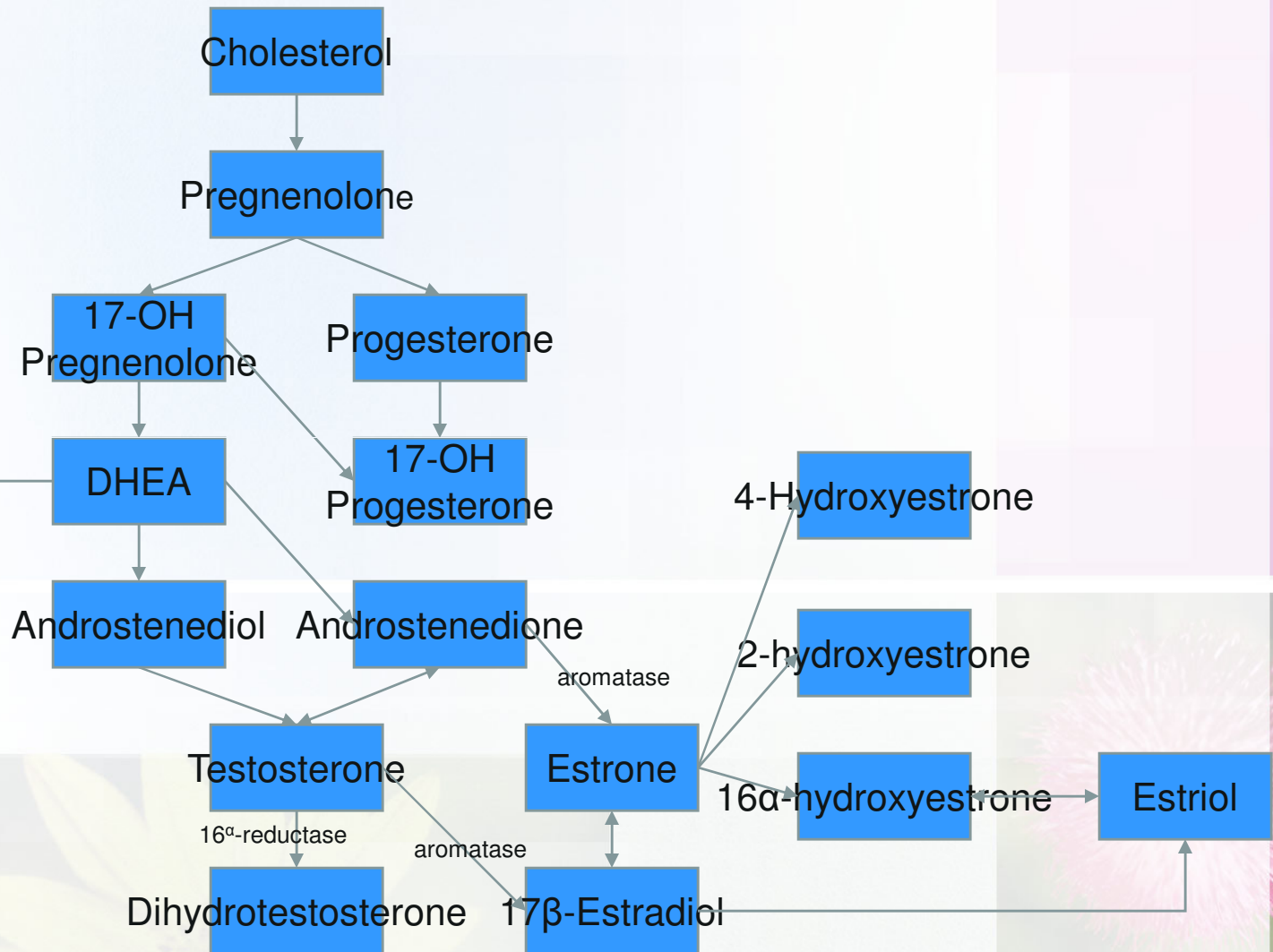
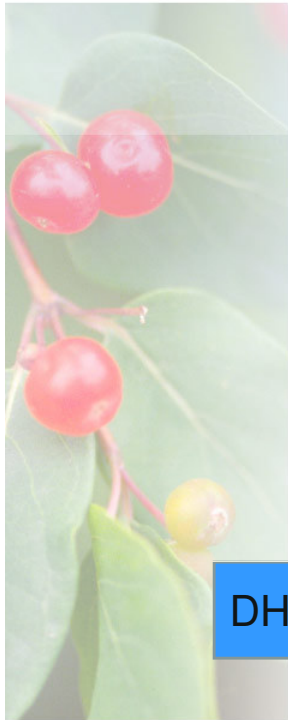
- **Estriol (E3)** – primary estrogen produced during pregnancy; weakest estrogen with 20-30% lesser affinity for the estrogen receptor in the cell; most is converted from estrone in the liver; small amount converted from estradiol; even smaller amount may be secreted directly from the ovaries

International Journal of Pharmaceutical Compounding, 2000 Nov/Dec;4(6)

- **Progesterone** - produced by ovocytes
- **Testosterone** – produced in adrenals, ovaries, liver, skin, and brain
- **DHEA** – produced in adrenals



Sex Hormone Metabolism



Estrogen Receptor Locations



- Vagina
- Cervix
- Uterus
- Oviducts
- Skin
- Bladder
- Hair
- Bone
- Central nervous system
- Cardiovascular system
- Lungs

Am J Physiol. 1996 Jan;270(1 Pt 1):L110-4

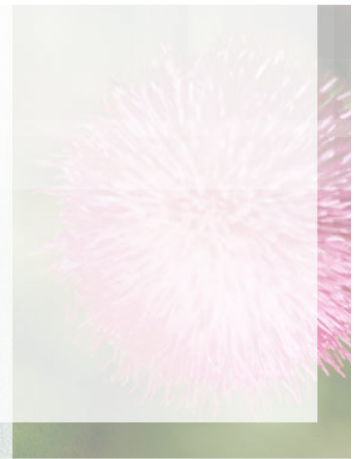
Experimental Biology © 2004 - Translating the Genome,
Abstract #'s 4241 and 7433, Massaro et. al., Georgetown U.
School of Medicine

- Thyroid
- Breast

Progesterone Receptor Locations



- **Bone**
- **Central Nervous System**
- **White Blood Cells**
- **Lungs**
- **Uterus**
- **Breast**
- **Colon**



Additional Progesterone Actions



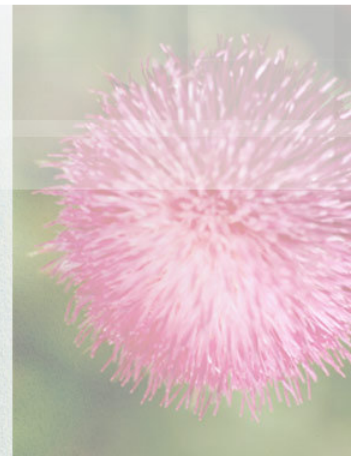
- Besides acting at the receptor sites, progesterone also**
- **Acts as a natural diuretic**
 - **Promotes thermogenesis**
 - **Aids thyroid hormone action**
 - **Helps stabilize blood sugar**
 - **Normalizes zinc and copper ratios**
 - **Promotes proper cell oxygen levels**

Wright and Morgenthaler, Natural Hormone Replacement for Women Over 45, ©1997, p.67



Treatment At The Jace Wellness Center

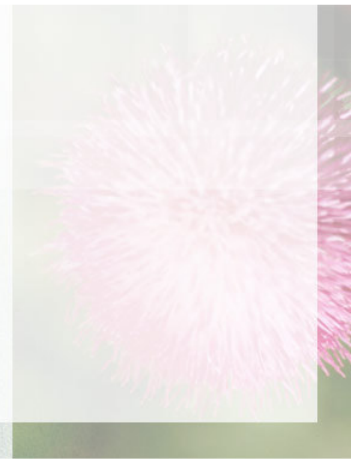
With Bio-Identical Hormones



Possible Treatment Interventions At The Jace Wellness Center

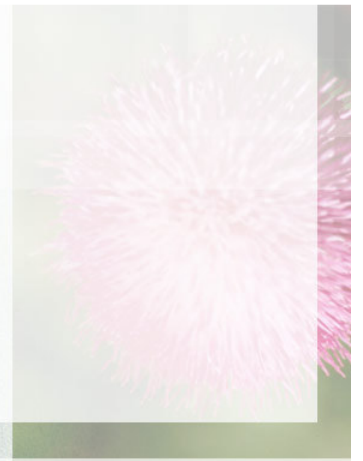


- **Diet, Nutritional Therapy**
- **Herbs, Acupuncture, Injections**
- **Bio-Identical Hormone Replacement Therapy**
- **Non-Bio-Identical Hormone Replacement Therapy if conditions are severe**





Bone Health



Osteoporosis Prevention



- Rule-out low stomach acid
- Weight bearing exercise
- Stop smoking
- Minimize alcohol, caffeine, animal protein, high phosphorus drinks, and grain consumption
- Increase consumption of whole fruits and vegetables
- Major nutrients: calcium, magnesium, vitamin D, strontium, vitamin K
- Minor nutrients: boron, zinc, copper

Estrogen and Bone



- Reduces the rate of activation of bone remodeling
- May correct the imbalance between resorption and formation
- May influence responsiveness to parathyroid hormone

Wise, Phyllis M., The female reproductive system in *Physiological Basis of Aging and Geriatrics, Third Edition*, Timiras, Ed copyright 2003 by CRC Press LLC, p.202

Low-dose Estradiol and Bone

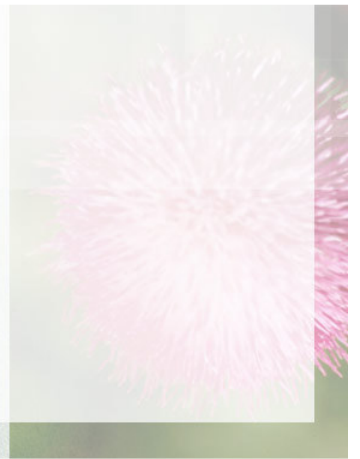


- 3 years of treatment with 0.25 mg/d of micronized 17beta-estradiol in healthy postmenopausal women over 65 years of age
- All women who had not had a hysterectomy received 100 mg/d of oral micronized progesterone for 2-week periods every 6 months
- Compared with participants receiving placebo, participants taking low-dose estrogen had BMD increases of 2.6% for the femoral neck; 3.6%, total hip; 2.8%, spine; and 1.2%, total body
- N-telopeptides of type 1 collagen and bone alkaline phosphatase decreased significantly ($P < .001$) in participants taking low-dose estrogen compared with placebo
- No statistically significant differences in breast tenderness, changes in endometrial thickness or pathological effects, or annual mammographic results between the 2 groups
- Number of abnormal mammograms over 3 years was 15 for the low-dose estrogen group and 10 for the placebo group (8 occurred at baseline) ($P = .26$); there were no reports of breast cancer during the study

JAMA. 2003 Aug 27;290(8):1042-8



Cardiovascular System



Cardiovascular Disease Prevention



- Eliminate refined carbohydrates, trans-fatty acids, and saturated fat
- Focus on whole fruits, vegetables, grains, nuts/seeds, and fish
- Aerobic and non-aerobic exercise
- Rule out Insulin Resistance
- Monitor levels of total cholesterol, HDL, LDL, triglycerides, hs-CRP, Homocysteine, and Fibrinogen
- Monitor blood pressure
- Stop smoking
- Major nutrients: Omega 3 fatty acids, Vitamin E, Coenzyme Q10



Estrogen and Vasculature



- **Incidence of cardiovascular disease is 1 in 9 in women aged 45 to 64, but rises to 1 in 3 in women over 65**
Eur. Heart J. 1996;17(15)
- **At menopause, the rate of myocardial infarction increases threefold, irrespective of age at menopause**
Matthew, K.A., Kuller, L.H., and Sutton-Tyrrell, K., Changes in cardiovascular risk factors during the peri- and postmenopausal years, in *Proceedings of the International Symposium on the Biology of the Menopause*, Bellino, F.L., Ed., Springer, Norwell, MA, 2000
- **Incidence of cerebrovascular disease rises rapidly at menopause**
Kannel, W.B. and Thom, T.J., The incidence, prevalence and mortality of cardiovascular disease, in *The Heart*, Schlant, R.C. and Alexander, R.W., Eds., McGraw-Hill, New York, 1994
- **Estrogen appears to decrease the progress of atherosclerosis and maintain arteriolar tone and integrity decreasing the risk of cardiovascular disease and cerebrovascular stroke**
Wise, Phyllis M., The female reproductive system in *Physiological Basis of Aging and Geriatrics, Third Edition*, Timiras, Ed copyright 2003 by CRC Press LLC, p.205
- **Levels of total and LDL cholesterol and triglycerides increase, while levels of HDL lipoproteins decrease during menopause**
Eur. J. Clin. Invest. 1997;27(322)
- **Levels of apolipoprotein A-I, a major protein component of HDL, decrease with menopause**
Wise, Phyllis M., The female reproductive system in *Physiological Basis of Aging and Geriatrics, Third Edition*, Timiras, Ed copyright 2003 by CRC Press LLC, p.205
- **Premenopausal women have enhanced arterial vasodilatation**
Wise, Phyllis M., The female reproductive system in *Physiological Basis of Aging and Geriatrics, Third Edition*, Timiras, Ed copyright 2003 by CRC Press LLC, p.205

Ischemia with E2 and Progesterone

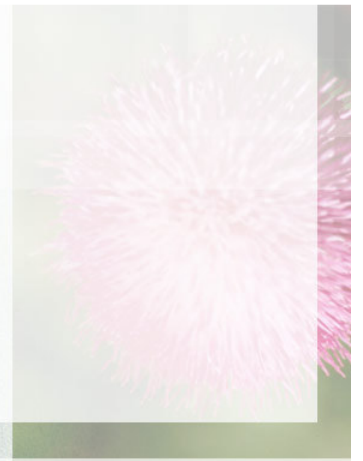


- Eighteen postmenopausal women 52-63 years of age studied for 4 weeks in a single-blinded manner
- 17 β -Estradiol at 1 mg/day for three weeks then 2 mg/day for one week. Estradiol (2 mg/day) was then continued, and the patients were randomized (double-blind) for 12 days to either transvaginal progesterone gel (90 mg on alternate days) and oral MPA placebo (10 mg/day), or vice versa. After another two weeks on estradiol alone, the patients crossed over to progestin treatment and repeated the protocol on the opposite treatment
- Exercise time to myocardial ischemia increased after the first estrogen phase as compared with baseline and was increased by combination estradiol/progesterone therapy as compared with estradiol/MPA therapy. Two patients were withdrawn while taking estradiol/MPA owing to unstable angina
- Combination estrogen/transvaginal progesterone gel increases exercise time to myocardial ischemia, as compared with estrogen/MPA

J Am Coll Cardiol. 2000 Dec;36(7):2154-9



Cognitive Health



Estradiol and Alzheimer's

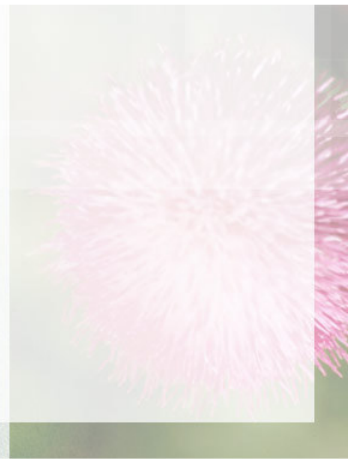


- Placebo-controlled, double blind, parallel-group design study
- 20 women randomized to receive either 0.10 mg/day of transdermal 17beta-estradiol or a placebo for 8 weeks
- APP, amyloid-precursor protein, is believed to play an important role in the pathobiology of Alzheimer disease (AD)
- Evaluated the effects of estradiol administration on plasma concentrations of one by-product of APP processing, Abeta40, for postmenopausal women with AD
- Results show preliminary clinical evidence to support an effect of estradiol on Abeta-processing for AD women who are HRT-naive. This finding suggests that the hormone may serve as an Abeta-lowering agent for HRT-naive AD women, which may, in turn, have ultimate ramifications for the progression of AD pathology

Am J Geriatr Psychiatry. 2003 Mar-Apr;11(2):239-44



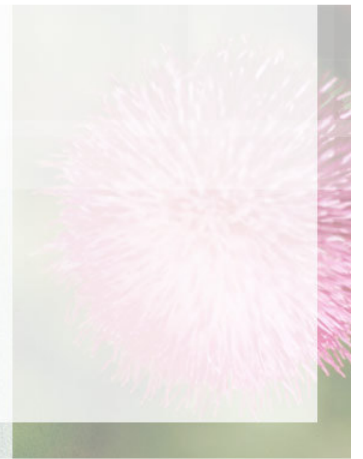
Breast Health



Breast Cancer Prevention

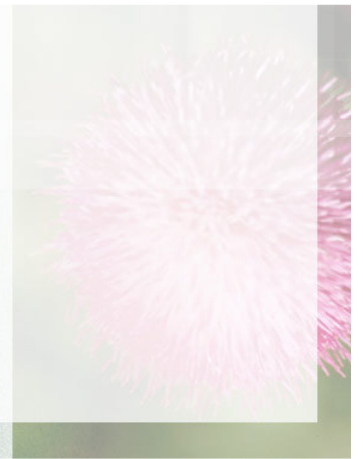


- Diet low in fat, high in fiber, high in fruits and vegetables, and low in fried foods, nitrites, and chlorinated water
- Folic Acid
- Cod Liver Oil
- Curcumin
- Vitamin D
- Selenium
- Iodine
- Multivitamin/mineral





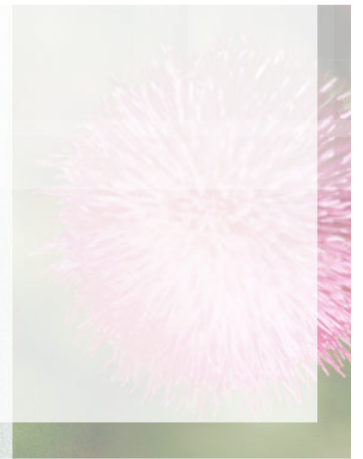
Colon Health



Colon Cancer Prevention

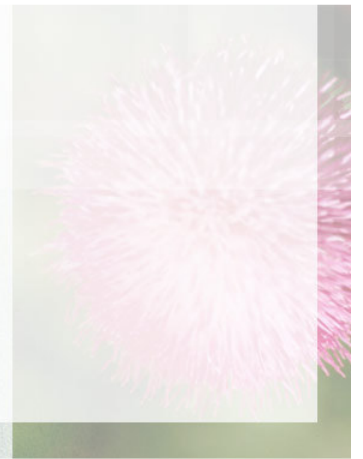


- **Diet low in fat, high in fiber, high in fruits and vegetables, and low in fried foods, nitrites, and chlorinated water**
- **Vitamin D**
- **Cod Liver Oil**
- **Folic Acid**
- **Psyllium or other fiber**
- **N-Acetyl-L-Cysteine**
- **Multivitamin/mineral**





Cervical Health



Cervical Cancer Prevention



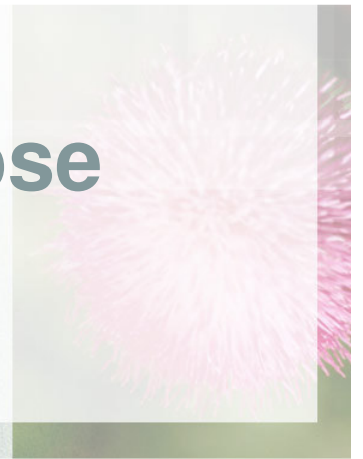
- **Folic Acid**
- **I-3-C**
- **Daily raw cabbage and/or brussels sprouts**
- **Vitamin C**
- **Vitamin A**
- **Green tea, alpha-tocopherol, CoQ10, and cis-lycopene**



Source of Bio-Identical Hormones



- **Diosgenin from Mexican Wild Yam root**
- **Beta sitosterol from soybean**
- **Extracted from plant in laboratory and made into iso-molecular compound**
- **Shipped to compounding pharmacy**
- **Pharmacy individualizes dose according to physician's prescription**

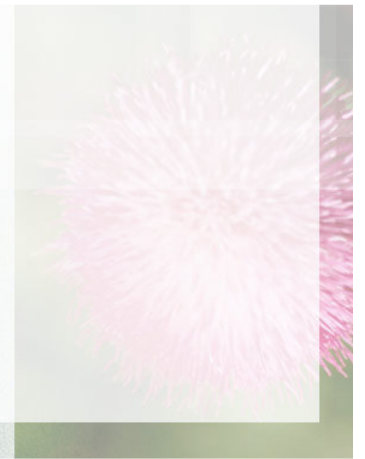


Possible Side Effects



- **Estrogen**
headache
breast tenderness
- **Progesterone**
drowsiness
- **Testosterone**
acne
hair growth
voice change
aggression

- **DHEA**
acne
hair growth
voice change
aggression



With or Without Food?



- **Absorption of micronized progesterone is enhanced twofold when the hormone is taken with food**

Fertil Steril 1993;60:26-33

- **If using other oral bio-identical hormones, take between meals**

Key Pharmacy in Kent, WA; July 2004

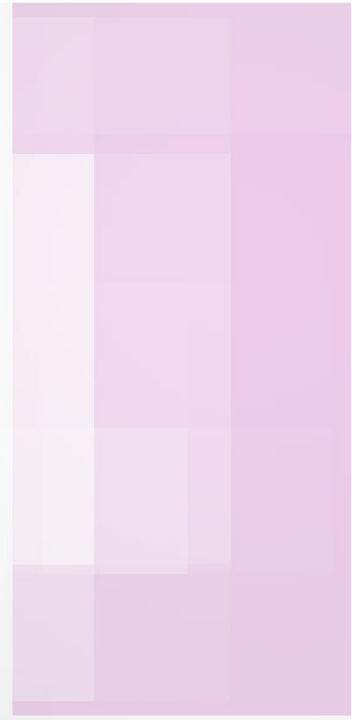
Exams



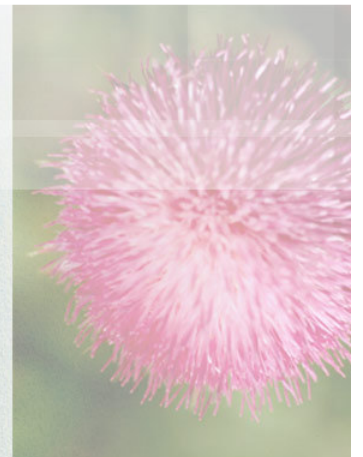
- Pap smear every 3 years if low risk; yearly if high risk
- Yearly gynecological exam and manual breast exam
- Monthly self breast exam
- Mammogram every 1-3 years (or mammogram every 5 years with thermogram yearly in between mammograms); baseline mammogram at age 40
- Fecal occult blood test yearly
- Fasting CBC with differential and serum lipid panel yearly
- DEXA at 65 years of age if no risk factors (<127lbs, nonvertebral fx after menopause, hx first-degree relative hip or vertebrae fracture, personal medical cause of bone loss); reevaluate every 18-24 months if abnormal
- Colonoscopy at 50 years of age and every 10 years thereafter if WNL
- Hormone levels at 2 months after starting bio-identical HRT and at least every 6 months thereafter if hormone levels are within normal range



Testing At The Jace Wellness Center

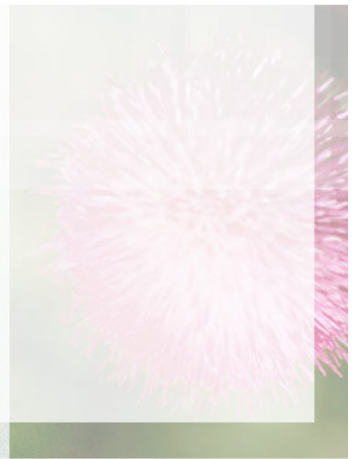


What is the best form of evaluation?





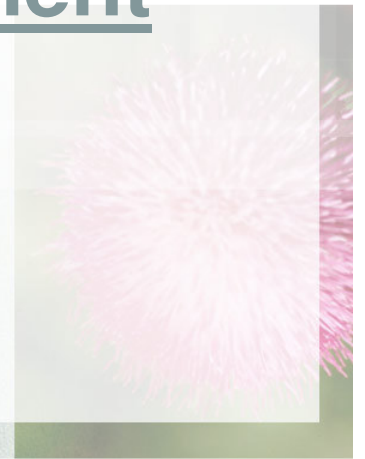
Saliva?



Testing levels of Hormones - Saliva



- Measures free and conjugated estrone, estradiol, estriol progesterone, testosterone, and DHEA
- Yields unphysiological levels when women are using bio-identical hormone replacement therapy; this gives a false impression of overdosing



Testing levels of Hormones - Saliva



- Most studies on transdermal progesterone demonstrate absorption through the skin
- Even though the studies also demonstrate symptom relief, serum levels remain low
- On the other hand, if using oral progesterone, serum levels rise
Menopause. 2003;10(1):3



Reliability of Saliva Testing

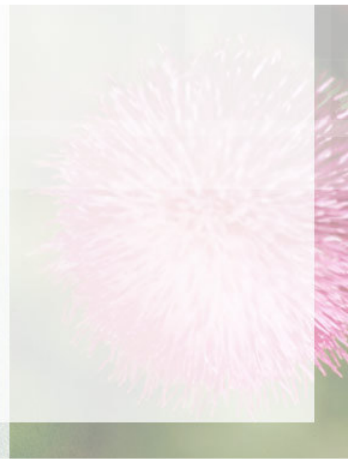


- Three participants and two labs
- Two women each provided three identically collected saliva samples to each lab
- One man provided one sample to each lab
- Fictitious names and demographics were used to blind the study
- Striking variation in results within each laboratory for each participant
- Within-subject coefficients of variation were 35-73% for estradiol, 8-103% for progesterone, and 13-40% for testosterone
- Each laboratory claimed to have a normal between-assay coefficient of variation of 8-12%
- Findings suggest laboratory values for saliva hormone samples collected with at-home test kits are not reliable

Journal of the American Pharmacists Association 2003;43(6):724 - 726



Urine?



Testing levels of Hormones - Urine

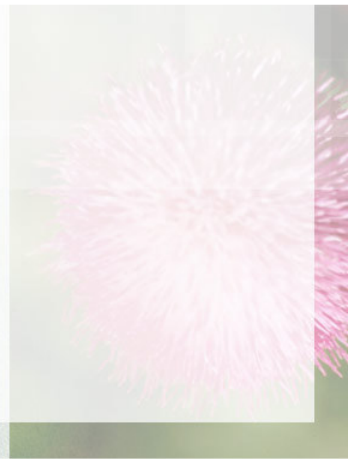


- Measures free estrone, estradiol, estriol, pregnanediol (progesterone), testosterone, and DHEA
- Does not measure total hormones levels, which includes protein-bound hormones
- Relatively accurate for women on or off bio-identical hormone replacement therapy





Blood?



Testing levels of Hormones - Blood



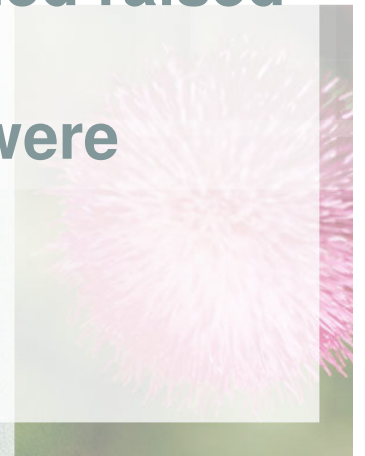
- Measures total estrone, estradiol, progesterone, testosterone, and DHEA
- Relatively accurate for women on or off bio-identical hormone replacement therapy
- Pro – free testosterone can also be measured
- Con - estriol usually only available as unconjugated and not as conjugated or total estriol (90% of estriol is conjugated)
- Con – free estrone, free estradiol, and free progesterone are rarely measured
- Con – one time blood draw within 24H

Testing levels of Hormones - Blood



- Oral administration of 100 mg daily for five consecutive days to 5 postmenopausal women
- Maximal plasma concentrations of progesterone within four hours after ingestion of the last dose, when the range was comparable with that observed during the mid-luteal phase of the ovarian cycle
- Surge in values lasted six hours, and progesterone concentrations remained raised for at least 96 hours
- Plasma concentrations of estradiol were unchanged by giving progesterone

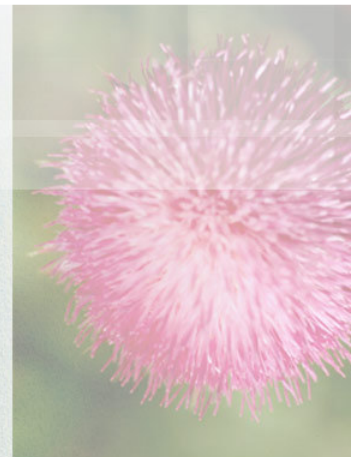
Br Med J. 1980 Mar 22;280(6217):825-7





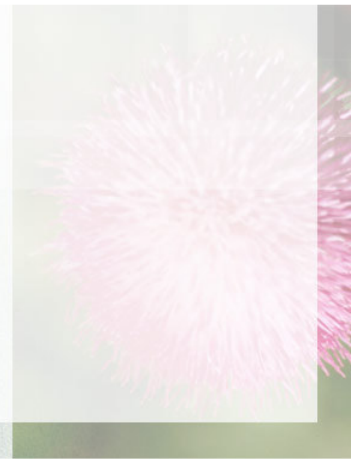
STUDIES

Safety of Bio-Identical Hormones





Breast Cancer



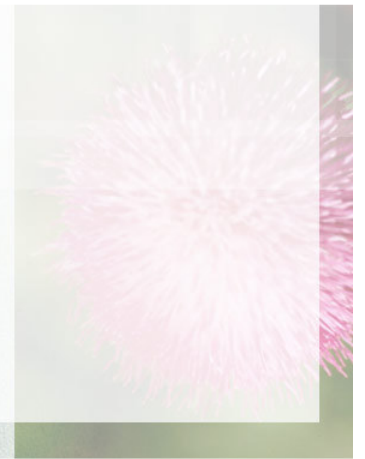
Urinary Estrogen and Breast Cancer



**For post-menopausal women,
Relative risk (highest/lowest
quartile)**

Estrone	2.5	(CI 1.6-3.8)
Estradiol	1.5	(CI 1.0-2.3)

Br J Cancer 2003;88:1394



Serum Estrogen and Breast Cancer



For post-menopausal women

Relative risk (highest/lowest tertile)

Estrone	4.1	(CI 1.4-11.9)
Estrone*	23.8	(CI 3.5-161)
Estradiol	3.6	(CI 1.3-10.0)

***ER+ patients only**

Clin Cancer Research 2003;9:2229

Ann Intern Med 1999;130:270

Estradiol



Million Women Study

- 24% increase in breast cancer risk with estradiol alone
- 29% increase with CEE alone
- 100% increase with Estrogens with Progestins (not Progesterone)
- The relative risks were increased separately for oral, transdermal, and implanted estrogen-only formulations (1.32 [1.21-1.45]; 1.24 [1.11-1.39] and 1.65 [1.26-2.16], respectively)

Lancet. 2003 Aug 9;362(9382):419-27

Estradiol gel and Breast Cancer



- France
- Cohort including 3175 postmenopausal women followed for a mean of 8.9 years (28,367 woman-years).
- 1739 (55%) of these women were users of one type of estrogen replacement with systemic effect during at least 12 months, any time after the menopause
- 83% were receiving exclusively or mostly a combination of a transdermal estradiol gel and a progestin other than MPA
- Some 105 cases of breast cancer occurred during the follow-up period, corresponding to a mean of 37 new cases per 10,000 women/year
- Using multivariate analysis adjusted for the calendar period of treatment, date of birth and age at menopause, they were unable to detect an increase in the relative risk (RR) of breast cancer (RR 0.98, 95% confidence interval (CI): 0.65-1.5) in the HRT users. The RR of breast cancer per year of use of HRT was 1.005 (95% CI 0.97-1.05)

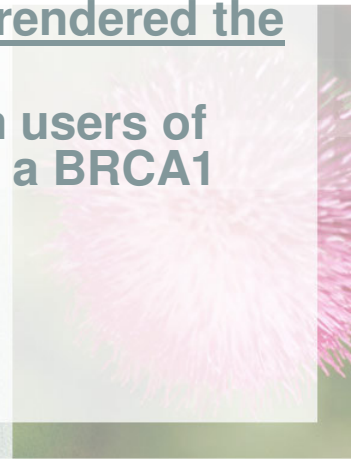
Climacteric. 2002 Dec;5(4):332-40

Bio-identical vs. Non Bio-identical and Continuous vs. Sequential



- Sweden
- Interview with population-based cohort of 29,508 women (298,649 person-years)
- In women with natural menopause, a significantly higher risk was observed for longer duration of combined continuous non bio-identical HRT use compared with never users
- Highest risks were associated with the combined continuous and progestin-only therapy in women with 48 months of use
- Nonsignificant elevated risks also were observed for longer combined sequential, progestin only, and estriol use
- Use of estradiol without progestins did not increase breast carcinoma risk significantly
- Continued use of progestins (not progesterone) rendered the highest risks
- The yearly risk of breast carcinoma for long-term users of progestins is of the magnitude of 50% the risk of a BRCA1 mutation carrier

Cancer 2003;97:1387-92



Estriol and Breast Cancer



PROSPECTIVE STUDY OF ESTROGENS DURING PREGNANCY AND RISK OF BREAST CANCER

by Pentti K. Siiteri, Robert I. Sholtz, Piera M. Cirillo, Richard D. Cohen, Roberta E. Christianson, Barbara J. van den Berg, William R. Hopper, and Barbara A. Cohn

Population: 15,000 pregnant women from 1959 and 1967

Type: prospective case-cohort study with 40-year follow-up

Results: protective association for the percent of estrogens present as estriol; The protective association increased monotonically by quartile of estriol percent. Breast cancer risk was reduced by 58% for the 4th quartile of estriol percent compared to the 1st quartile of estriol percent (95% CI=26% reduction to 77% reduction).

Conclusion: findings consistent with an earlier hypothesis that estriol, an estrogen largely of fetal origin that rises 1,000-fold during pregnancy, protects against maternal breast cancer by antagonizing the effects of the active estrogen, estradiol.

http://cdmrp.army.mil/bcrp/era/abstracts2002/p13_chemoprevention/9919358_abs.pdf

Ann Neuro. 2002 Aug 19;52(4):421-428

Estriol



Shown to have agonist & antagonist activity

- Estriol acts as a weak estrogen when administered in a single dose into immature or ovariectomized laboratory animals, but produces full estrogenic responses upon chronic administration. However, when estriol is injected together with estradiol it acts as an antiestrogen.

Mol Endocrinol. 1997 Nov;11(12):1868-78

- Estriol acts as an estrogen antagonist when injected as a bolus because of the short nuclear retention time of nuclear receptor estriol complexes. However, when estriol is present continuously and nuclear receptor estriol complex is elevated and maintained, estriol is a potent estrogen without antagonistic properties.

Endocrinology. 1977 Jan;100(1):91-6

- Estriol emerges as a short-action agonist when administered in a single dose. It is also concluded that estriol may prevent 17-beta estradiol from inducing a full uterotrophic response.

Acta Endocrinol Suppl (Copenh). 1980;233:9-16

Breast Cancer and Testosterone

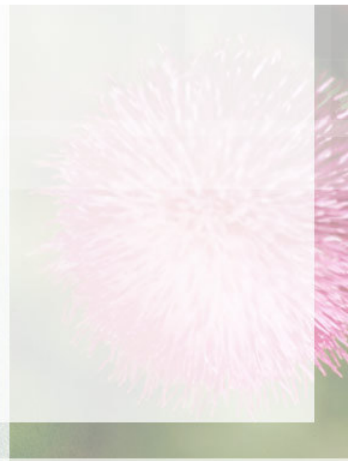


- Serum concentrations of estrone, androstenedione, testosterone, and sex hormone-binding globulin (SHBG) were measured postoperatively in 122 postmenopausal women with incident breast cancer and 122 age-matched population controls
- No association of testosterone with breast cancer risk
- Study reveals sharp contrasts in breast cancer risk between women with high estrone and low BMI and SHBG, vs. women with low estrone and high BMI and SHBG

Epidemiology. 1996 Jan;7(1):96-100



Endometrium



Progesterone and Endometrium



- 236 nonhysterectomized postmenopausal women; 79 women stopped before 5 years mostly due to symptom resolution and fear of side effects
- Observational clinical expanded case report
- 126 women received 1.5mg percutaneous estradiol for 21 days out of 28 and 200mg of oral micronized progesterone for the last 14 days of the estradiol treatment
- 23 women received 3mg percutaneous estradiol for 25 days out of 28 and 300mg of oral micronized progesterone for the last 10 days of the estradiol treatment
- 8 women received intermediate doses of estradiol and progesterone
- Uterine biopsy performed on every woman after at least 5 years of treatment
- “The antiproliferative effects seems to be sufficient because no hyperplasia was observed after 5-7 years exposure during treatment either by biopsy when endometrial tissue was available or by hysteroscopy when no endometrial tissue was available for biopsy”
- “Maximal reduction of mitoses was noted on biopsies taken after 11 days of progesterone treatment”

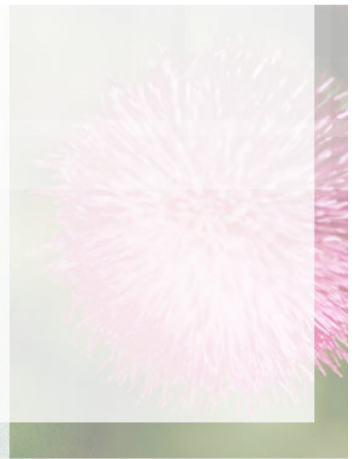
Fertil Steril. 1993 May;59(5):992-7

Life Expectancy



With prolonged life expectancy, men and women can expect to live one-third of their lives with some form of hormone deficiency

World J Urol. 2002 May;20(1):4-10





It is only when we live our life in the open, accept responsibility for the decisions that we have made, and own our behavior that we begin to know health.

- Unknown

