

The Necessity and Safety of Bioidentical Sex-Steroid Restoration in Women

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Topics

- ✦ Hormones and Aging
- ✦ Bioidentical vs. Pharmaceutical
- ✦ Estradiol/Progesterone Complementarity
- ✦ Breast Cancer
- ✦ Atherosclerosis and Thrombosis
- ✦ Osteoporosis
- ✦ The Problems with Hormone Substitutes
- If time: ✦ The Information War
- ✦ Pharmacy Compounding

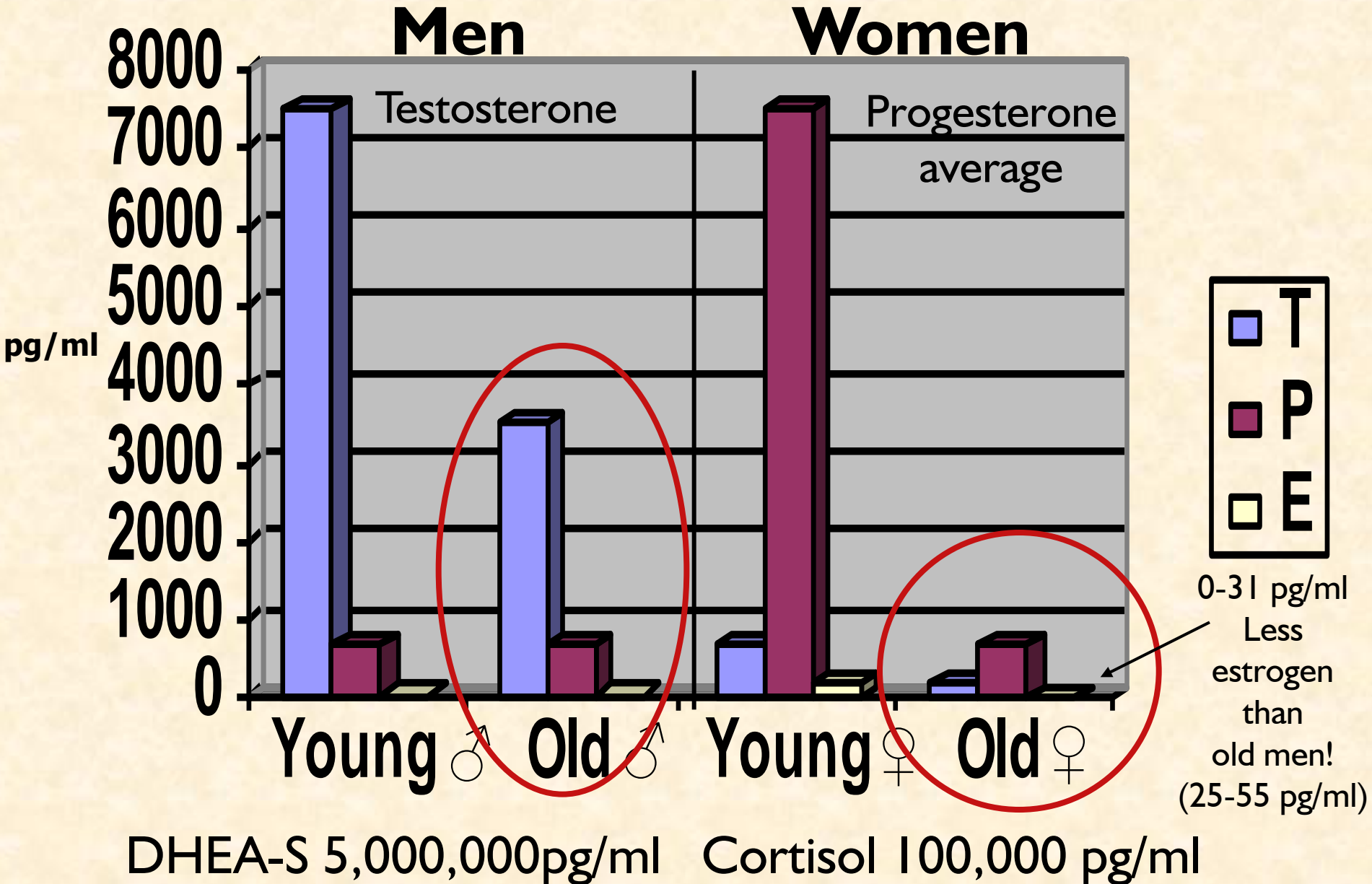
Main Points

- ✦ Estradiol replacement is medically necessary.
- ✦ Estradiol replacement is safe if transdermal and accompanied by sufficient progesterone.
- ✦ Testosterone and DHEA should also be restored to youthful levels.
- ✦ Problems caused by hormone substitutes have not been seen with balanced bioidentical sex-steroid restoration.
- ✦ The burden of proof lies with those who oppose bioidentical sex-steroid restoration for women.

Not Just “Sex Hormones”

- ✦ Estradiol, progesterone, testosterone and DHEA are required for the function, growth, and maintenance, of **all** tissues in **both sexes!**
 - ◆ **Maintain brain function and health**—neurosteroids—modulators of mood, cognition, memory, pain, etc.
 - ◆ **Maintain the immune system**—progesterone and testosterone are immunosuppressants
 - ◆ **Maintain connective tissue:** skin, hair, bone, muscle
 - ◆ **Improve insulin sensitivity**
 - ◆ **Reduce blood pressure**—improve endothelial function
 - ◆ **Prevent atherosclerosis**

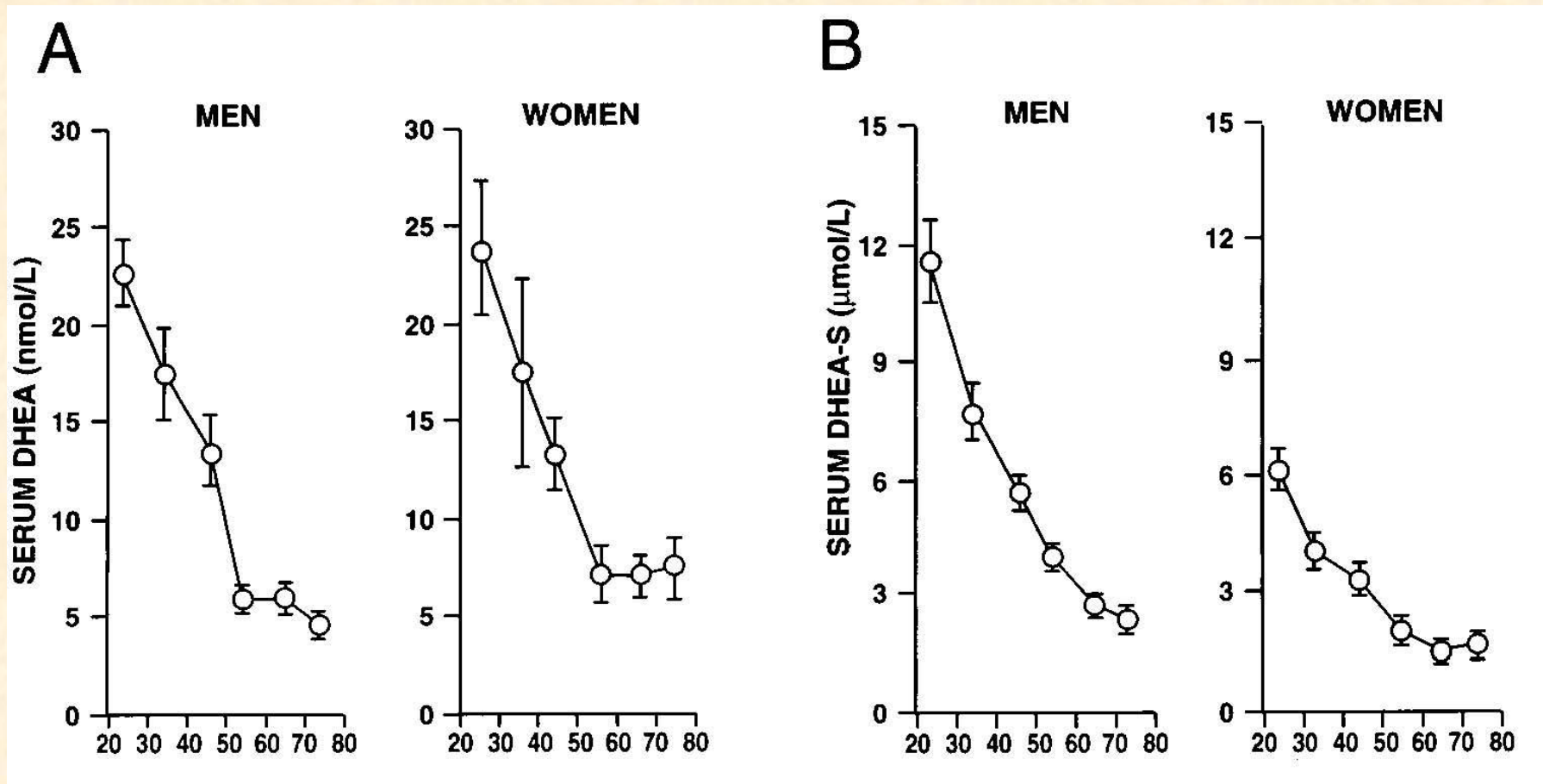
Steroid Loss in Women » Men



Adrenopause

DHEA ↔ DHEA-S

Substrate for extragonadal estradiol and testosterone synthesis



Hormone Loss with Age

- ✦ Common Assumption: Youthful levels good for hunting, fighting and reproduction but cause **heart attacks** and **cancer** later.
- ✦ ⇨ Hormone loss with age is adaptive—lengthens our lives.
- ✦ **But**: sex-organ **cancers**, **heart attacks**, and **osteoporosis** occur **years after** hormone levels start to decline;
- ✦ **And**: these diseases occur more often in people with **lower** hormone levels.

So Why do we Lose our Hormones?

- ✦ We are genetically programmed to die.
- ✦ Nature **kills** us, otherwise we would be immortal.
- ✦ Deterioration starts at age 25!
- ✦ **Aging is dying**; the universal “underlying disease”.
- ✦ Hormone loss is caused by and contributes to other mechanisms of **aging**.
- ✦ Age-related hormone loss both **natural** and **deleterious**.
- ✦ The symptoms of menopause are **warning signs** of worsening health.

Women Killers and Hormones

- ✦ Cardiovascular disease (CVD), osteoporosis, and breast cancer are all rare before menopause.
- ✦ All three diseases are clearly related to hormone deficiency or imbalance.
- ✦ Youthful estradiol/progesterone/testosterone hormonal milieu protects women from these diseases.

Menopause—Estradiol Deficiency

- ✦ Hot flashes
- ✦ Irritability, insomnia, depression
- ✦ Fatigue, aches and pains
- ✦ Poor memory, ↑'d risk of **Alzheimer's dementia**
- ✦ **Osteoporosis**→spine and hip fractures, loss of teeth
- ✦ **Genital atrophy**, vaginal dryness
- ✦ **Atrophy** of skin and connective tissue
- ✦ Endothelial **dysfunction**, ↑**blood pressure**
- ✦ **Atherosclerotic heart disease**

Estradiol Restoration

- ✦ Eliminates hot flashes, restores sleep
- ✦ Protects cognitive function, improves mood
- ✦ Maintains thickness, fullness of skin and hair
- ✦ Protects against colon cancer and macular degeneration
- ✦ Prevents atherosclerosis, hypertension
- ✦ Maintains genital/pelvic health
- ✦ Improves insulin sensitivity—helps diabetes
- ✦ Prevents osteoporosis and osteoarthritis
- ✦ Maintains gynecoid fat distribution

Female Andropause

- ✦ Young woman's free **testosterone** level in serum is **2x** her free **estradiol**
- ✦ Female **testosterone** levels **decline 50%** between age 20 and 40. Zumoff B, J Clin Endocrinol Metab. 1995 Apr;80(4):1429-30
- ✦ ERT → **↓DHEAS 23%**, **↓total testosterone 42%**
Casson PR, Obstet Gynecol. 1997 Dec;90(6):995-8
- ✦ BCPs → **↓DHEAS 30%**, **↓free testosterone 60%**
White T, Am J Obstet Gynecol. 2005 Jun;192(6):2055-9
- ✦ **DHEAS declines with age**—main source of androgen-effects in women.
- ✦ Lower free **testosterone** → **↑risk of heart attack** and **osteoporotic fractures**

Testosterone Restoration

- ✦ Improves energy, mood, well-being

Goldstat R, Menopause. 2003 Sep-Oct;10(5):390-8

- ✦ Improves sexual desire and sensation

- ✦ Improves muscle strength

- ✦ Improves insulin sensitivity

Miller KK, J Clin Endocrinol Metab. 2007 Jul;92(7):2474-9

- ✦ With **estradiol**, greater \uparrow in bone density

Davis SR, Maturitas 1995; 21:227-236

Miller BE, Menopause. 2000 Sep-Oct;7(5):318-26

- ✦ Improves flow-mediated arterial dilation

- ✦ Probably **decreases** risk of **heart attack**

Rako S, J Womens Health. 1998 Sep;7(7):825-9

Kaczmarek A, Int J Cardiol. 2003 Jan;87(1):53-7

- ✦ Opposes estradiol-induced breast stimulation and reduces risk of **breast cancer**.

DHEA

- ✦ Most abundant steroid hormone; yet **ignored**
- ✦ Cells make **testosterone** and **estradiol** from it
- ✦ Levels **decline** with age, stress and disease
- ✦ **Lower** levels assoc. with ↑disease, ↑mortality
- ✦ **Anabolic**—builds tissues, improves immunity
- ✦ Improves sexual function
- ✦ **Anti-cortisol effect, reduces** abdominal fat
- ✦ **Reduces pain**—restores natural endorphins
- ✦ **Reduces** inflammation (↓IL-6, TNF- α , ↑IL-2)
- ✦ **Anti-atherosclerotic**, prevents oxidation of LDL
- ✦ **Improves fertility** in older women-egg# and quality

Barad D, Brill H, Gleicher N. Update on the use of dehydroepiandrosterone supplementation among women with diminished ovarian function. J Assist Reprod Genet. 2007 Dec;24(12):629-34.

The Solution: Hormone Restoration

- ✦ If a hormone is **missing**, **replace it!**
- ✦ If present but **insufficient**, **optimize it!**
- ✦ Optimal levels improve both **health** and **quality of life**
- ✦ **Bioidentical**=correct chemical structure
- ✦ **Bioidentical**=Standard of Care: insulin, T₄, growth hormone, cortisol (hydrocortisone), oxytocin, etc.
- ✦ Must also optimize all **vitaminutrients**: Vit D, Omega-3 fatty acids, iron, other vitamins, minerals, etc.

Bioidentical Hormones are not Drugs

- ✦ **Optimal** levels **required** for health
- ✦ **Non-toxic**, **inherently safe**
- ✦ **No** allergic or idiosyncratic reactions
- ✦ **No** “side effects”, only effects!
- ✦ **Proper fit** in receptors, normal elimination
- ✦ **Monitor** therapy with blood tests! (not so with **Premarin[®]**, **Provera[®]**, **prednisone**, etc.)
- ✦ **Potential problems** with **bioidenticals**:
 - ◆ **Excessive** dose
 - ◆ Lack of **balance** with other hormones
 - ◆ **Unphysiological** delivery: route, timing, etc.

But won't bioidentical
hormone restoration cause
breast cancer, strokes, and
heart attacks?

Sex-Organ **Cancers** and the Female Burden of Reproduction

- ✦ Female organs and cyclic hormonal system exist for **reproduction**, not for the woman's health!
- ✦ Breast, uterine and ovarian tissues undergo a **monthly cycle** of proliferation, differentiation, and breakdown
- ✦ **Defects** in this cycle can lead to **cancers** in female organs and to many **medical disorders**.

Historical Perspective

- ✦ Throughout history, women were usually pregnant or breast feeding; both **protective** against **breast cancer**.
- ✦ Only **4 years** of cycling on average.
- ✦ Today, women may experience **35 years** of **cycling**
- ✦ Much greater risk of **progesterone deficiency**, **PCOS**, **breast**, **ovarian** and **uterine cancers**, and other diseases and disorders

Estradiol

- ✦ **Angel of Life**—stimulates growth of female organs necessary for reproduction; maintains female health and quality of life
- ✦ **Angel of Death**—promotes **cancer** and other medical disorders— **if not balanced** with **progesterone** and **androgens**

Estradiol-Progesterone Complementarity

- ✦ Estradiol promotes uterine and breast tissue proliferation and growth
- ✦ Progesterone **stops** proliferation and promotes maturation and differentiation.
- ✦ Progesterone withdrawal → sloughing and necrosis of uterine lining **and** breast duct epithelium.
Longacre TA, Am J Surg Pathol. 1986 Jun;10(6):382-93
- ✦ High persistent progesterone/estradiol ratio suppresses **proliferation** and prevents **cancers**.
- ✦ Inadequate progesterone = **estrogen dominance**

Progesterone's Anti-Estrogenic Actions in Uterus and Breast

- ✦ Decreases synthesis of estradiol receptors
- ✦ Increases conversion of estradiol to estrone (weak estrogen) by inducing 17 β -hydroxysteroid dehydrogenase Type 2
- ✦ Reduces conversion of estrone to estradiol by inhibiting 17 β -hydroxysteroid dehydrogenase Type 1
- ✦ Increases sulfation (inactivation) of estrogens

Progesterone vs. Breast Cancer

- ✦ Progesterone cream applied to the breast reduces proliferation.

Chang KJ, Fertil Steril 1995; 63:785-91

Barrat J, J Gynecol Obstet Biol Reprod (Paris). 1990;19(3):269-74

Foidart JM, Fertil Steril. 1998 May;69(5):963-9

- ✦ Estradiol is carcinogenic in breast cell cultures unless progesterone is present.

Russo J, J Steroid Biochem Mol Biol. 2003 Oct;87(1):1-25

- ✦ Normal breast cells proliferate after E2 treatment, but become quiescent when P is added.

Malet C, J Steroid Biochem Mol Biol. 2000 Jun;73(3-

4):171-81

Foidart JM, Fertil Steril. 1998 May;69(5):963-9

- ✦ Estrogen upregulates cancer-promoting gene bcl-2, progesterone downregulates it.

Formby B, Ann Clin Lab Sci. 1998 Nov-Dec;28(6):360-9

Progesterone vs. Breast Cancer

- ✦ Premenopausal women with **low progesterone** levels had 5.4x **risk** of early **breast cancer**

Cowan LD, Am J Epidemiol. 1981;114:209-17

- ✦ **Breast cancer** victims have **progesterone resistance**

Simpson HW, Br J Obstet Gynaecol. 1998 Mar;105(3):345-51

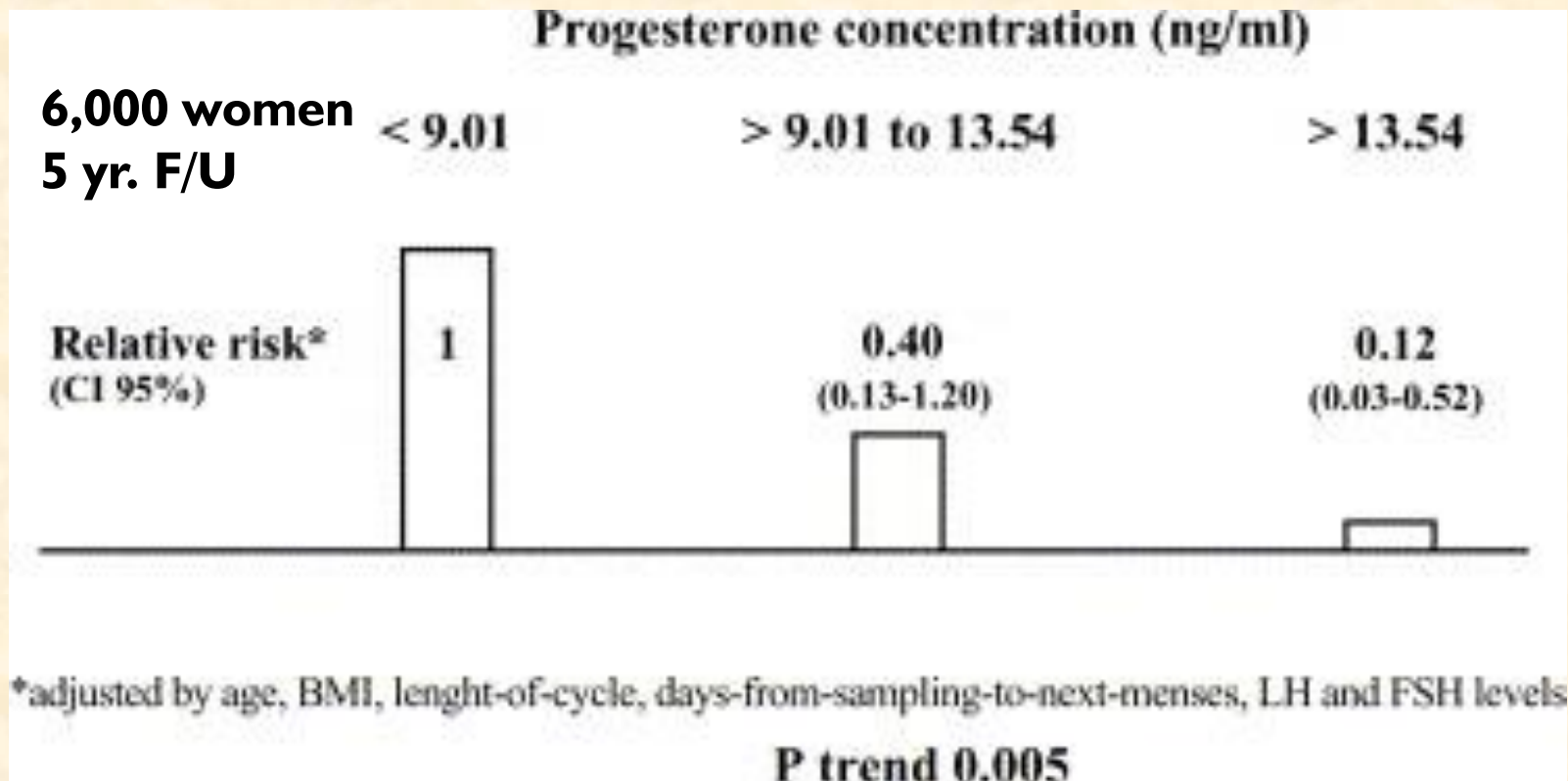
- ✦ **Progesterone** decreases proliferation and induces **apoptosis** in breast cancer cell lines.

Ansquer Y, Anticancer Res. 2005 Jan-Feb;25(1A):243-8
Groshong SD, Mol Endocrinol. 1997 Oct;11(11):1593-607

- ✦ **Progesterone** receptor positivity predicts better long-term survival with **breast cancer**

Costa SD, Eur J Cancer. 2002 Jul;38(10):1329-34
Lamy PJ, Breast Cancer Res Treat. 2002 Nov;76(1):65-71

Progesterone vs. Breast Cancer

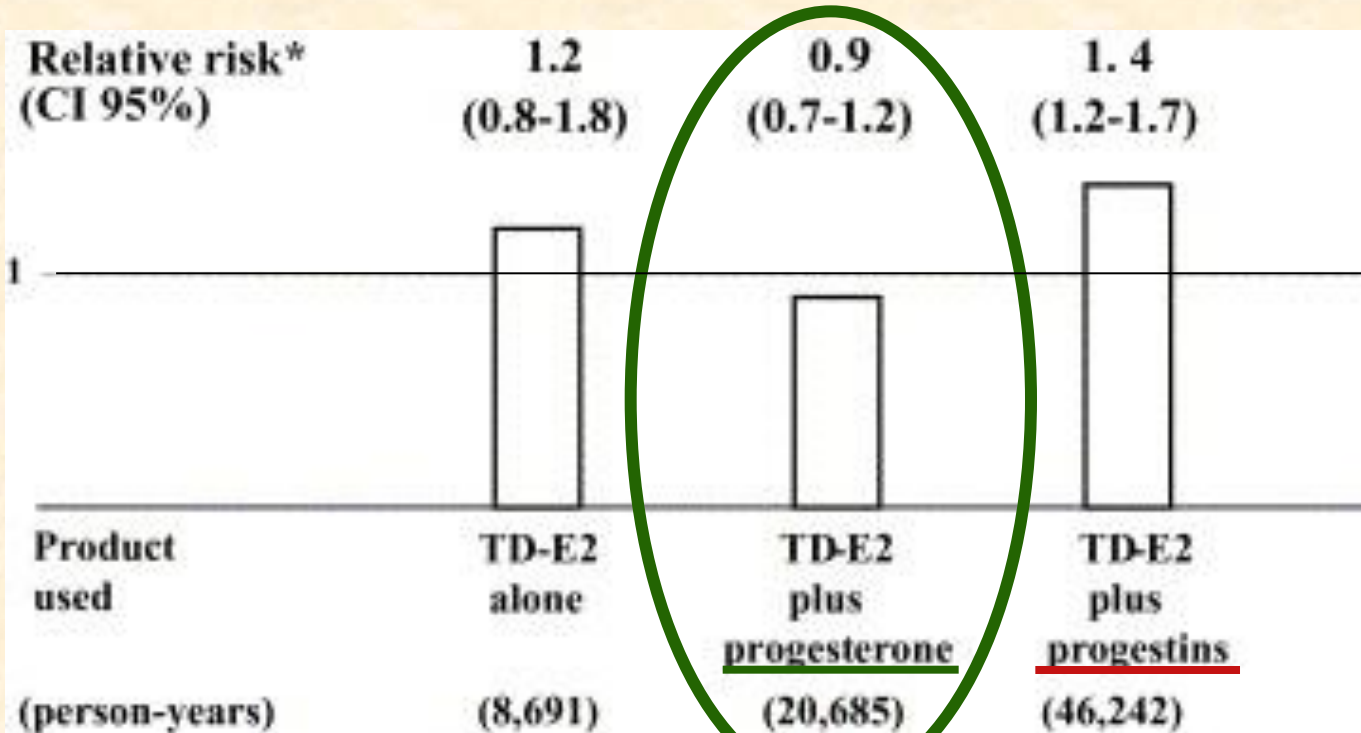


Higher progesterone = lower risk of breast cancer

E3N-EPIC Study

TD-E2 = transdermal **estradiol**

Cohort study
55,000 women
8 years f/u
c/w WHI--
16,000, 6 yr. f/u



Int J Cancer. 2005 Apr 10;114(3):448-54

E2 plus progesterone decreased risk of breast cancer!

See also: De Lignieres B, de Vathaire F, Fournier S, et al. Combined hormone replacement therapy and risk of breast cancer in a French cohort study of 3175 women. Climacteric 2002;5:332-40.

Progesterone is Innocent!

“The balance of the *in vivo* evidence is that progesterone does not have a **cancer-promoting effect on breast tissue.”**

Campagnoli C. Progestins and progesterone in hormone replacement therapy and the risk of breast cancer. J Steroid Biochem Mol Biol. 2005 Jul;96(2):95-108.

“The hypothesis of progesterone and some progesterone-like progestins decreasing the proliferative effect of estradiol in the postmenopausal breast remains highly plausible and should be, until the coming of new evidences, the first choice for symptomatic postmenopausal women.”

Modena MG, Sismondi P, Mueck AO, Kuttann F, Lignieres B, Verhaeghe J, Foidart JM, Caufriez A, Genazzani AR; The TREAT. Maturitas. 2005 Sep 16;52(1):1-10.

Estrogen Therapies and Breast Cancer

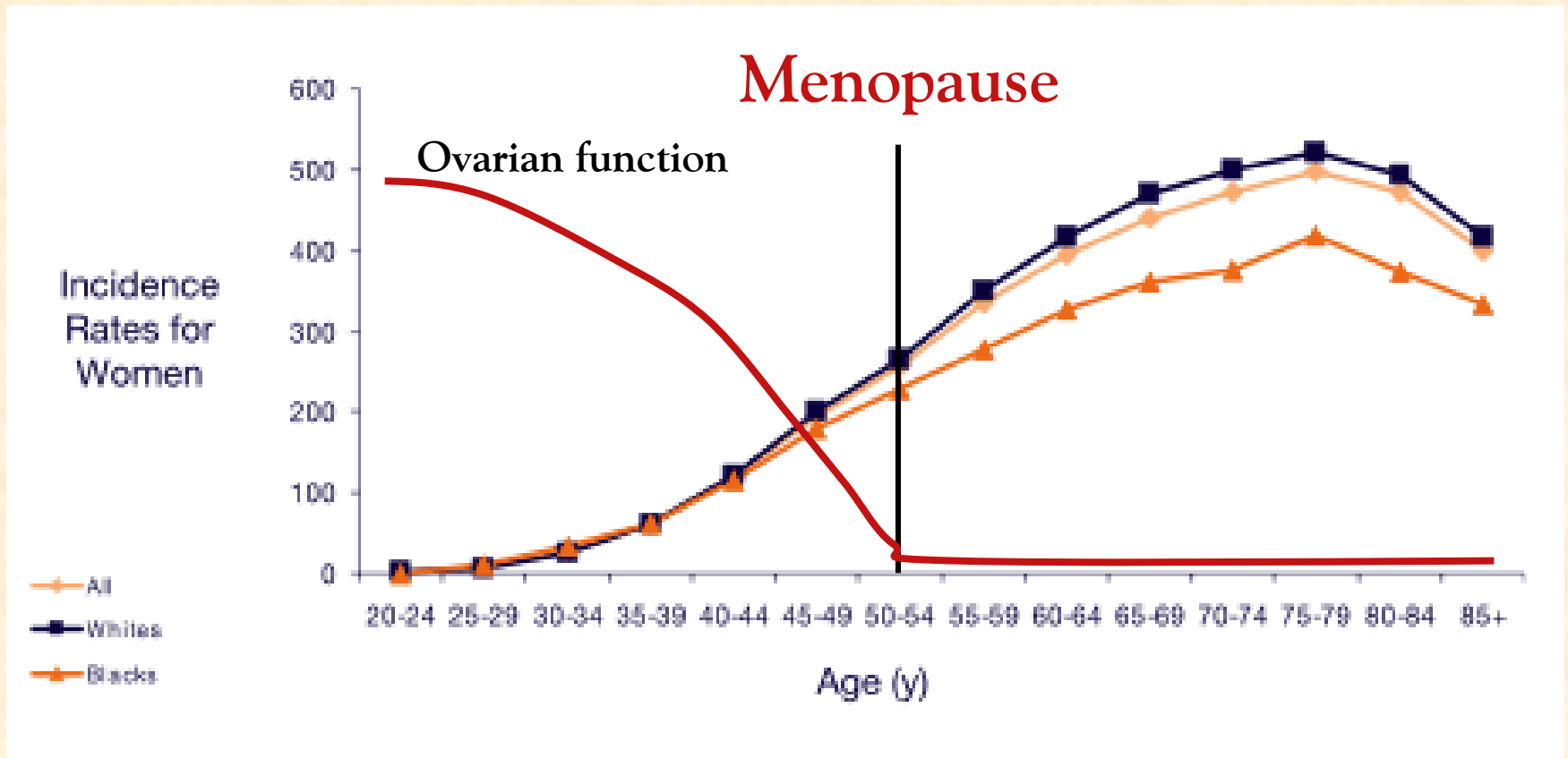
- ✦ Bulk of evidence shows small increase in **breast cancer** with unopposed estrogen (RR~1 to 1.2)
- ✦ Risk increased with estrogen/**progestin** combinations (RR~1.4-2.0)

Beral V, Million Women Study. Lancet. 2003 Aug 9;362(9382):419-27

- ✦ No ↑'d risk of **breast cancer** in Premarin[®]-only arm of WHI
- ✦ Risk may be higher with unopposed transdermal **estradiol** c/w Premarin[®]

Breast Cancer Rate vs. Age

Loss of progesterone → higher risk of breast cancer



The Key—Intramammary Steroids

- ✦ Breast tissue can produce **estradiol** locally from adrenal androgens (**DHEA, androstenedione**)
- ✦ Compared to the premenopausal breast, postmenopausal breast nipple aspirate fluid has:
 - ✦ Same estradiol concentration (high youthful serum conc.)
 - ✦ Much lower progesterone concentration

Chatterton RT Clin Endocrinol Metab. 2005 Mar;90(3):1686-91

- ✦ Breast must get **progesterone** from blood, and concentrates it by a factor of 3-4x.

Gann PH, Cancer Epidemiol Biomarkers Prev. 2006 Jan;15(1):39-44

- ✦ No luteal **progesterone** → intramammary **estrogen dominance** → **breast cancer**.

Progesterone Deficiency States

- ✦ With aging, remaining oocytes are of lower quality
- ✦ There is **reduced** luteal **progesterone** production beginning as early as age 30→**estrogen dominance**
- ✦ Luteal phase insufficiency→**estrogen dominance**
- ✦ Anovulation→**estrogen dominance**
- ✦ Menopause→intramammary **estrogen dominance**
- ✦ Progesterone replacement is necessary in all these states.

Progesterone Deficiency → Estrogen Dominance

- ✦ Allergies
- ✦ Autoimmune diseases
- ✦ Anxiety, irritability
- ✦ Insomnia
- ✦ Depression
- ✦ Bloating and edema
- ✦ Fibrocystic breasts
- ✦ Uterine fibroids
- ✦ Breast cancer
- ✦ Ovarian cancer
- ✦ Uterine cancer
- ✦ Thyroid dysfunction
- ✦ Gallbladder disease
- ✦ Menorrhagia
- ✦ Migraines
- ✦ Seizures

Progesterone restoration is the preventative and corrective treatment.

Endogenous Hormones and Breast Cancer

- ✦ DHEAS and testosterone can be converted into estradiol within the breast.
- ✦ Some studies show increased **breast cancer** risk with ↑'d testosterone and DHEAS levels.

Kaaks R (EPIC). J Natl Cancer Inst. 2005 May 18;97(10):755-65

Key T, . J Natl Cancer Inst. 2002 Apr 17;94(8):606-16

- ✦ Confounder: Premenopausal disorders causing ↑'d testosterone and DHEAS are associated with low progesterone levels (PCOS).
- ✦ Postmenopause: DHEAS and testosterone can be converted into estrogen and increase risk of **breast cancer** unless progesterone is restored.

Testosterone Prevents Breast Cancer in Estradiol-Replete Women

- ✦ Testosterone opposes estradiol-induced **breast stimulation**.

Dimitrakakis C, Menopause. 2003 Jul-Aug;10(4):292-8

Somboonporn W, Endocr Rev. 2004 Jun;25(3):374-88

Zhou J, FASEB J. 2000 Sep;14(12):1725-30

- ✦ Addition of **testosterone** to estrogen/progestin reduces **breast cancer** incidence to baseline.

508 women; 8 yrs.

Dimitrakakis C, Menopause. 2004 Sep-Oct;11(5):531-5

- ✦ **Testosterone** and **DHT** inhibit *in vitro* growth of **breast cancer** cells.

Ortmann J, Gynecol Endocrinol 2002; 16: 113-120

- ✦ **Testosterone** is an effective treatment for **breast cancer**.

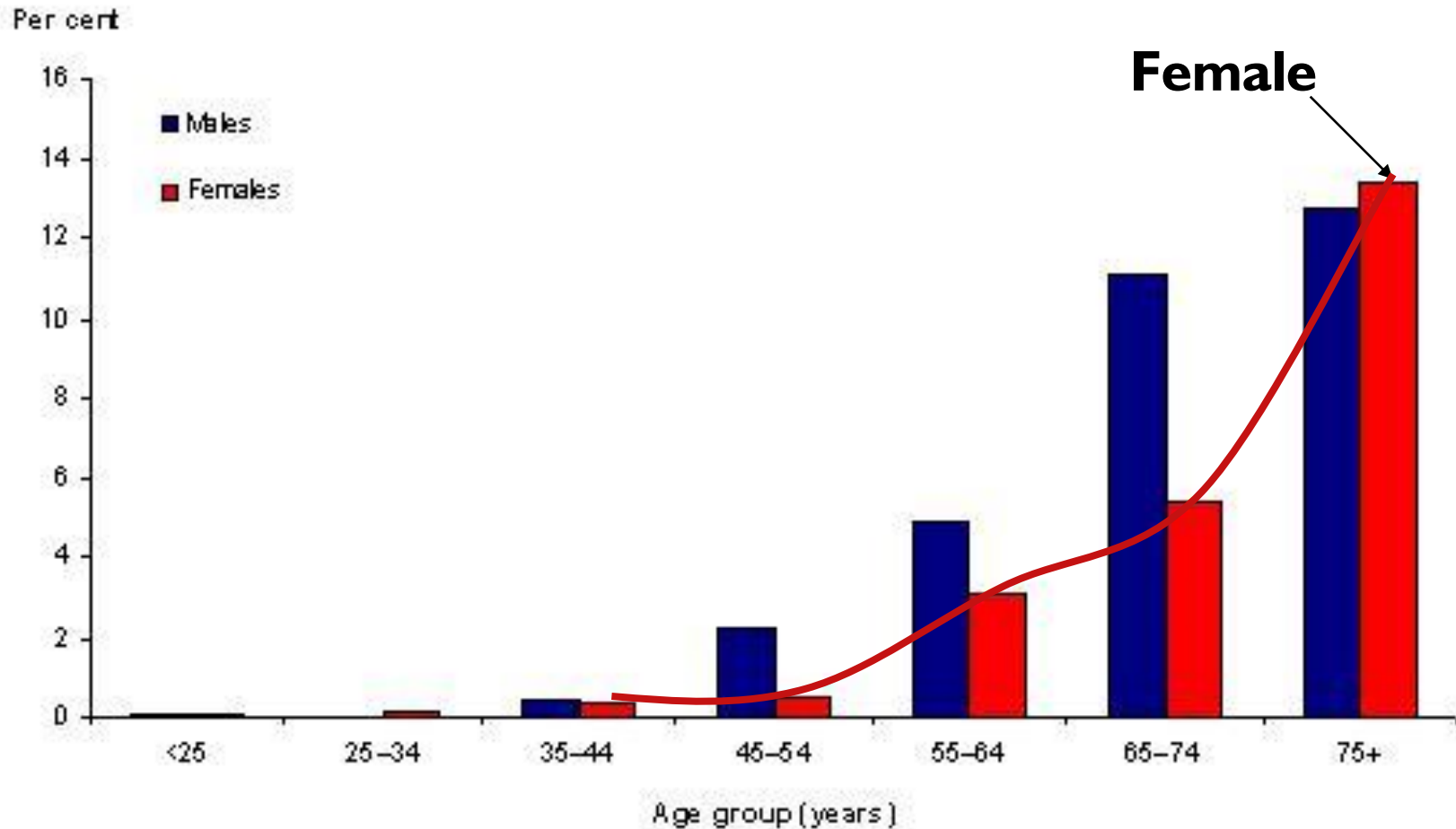
Labrie F, Cancer Detect Prev. 1992;16(1):31-8 (review)

CAD and Female Hormones

- ✦ Natural estradiol and progesterone production are highly **protective** against CAD.
- ✦ Youthful/healthy hormonal milieu is **protective**.
- ✦ After menopause, women's rate of **CVD rises faster** than men's! Higher risk than men after 65, and higher mortality after 70!
- ✦ Surgical menopause → ↑ **mortality**, ↑ **atherosclerosis**, **2-7x** risk of **heart attacks**; earlier age → greater risk

Colditz GA, Engl J Med 1987 Apr 30;316(18):1105-10
Rosenberg L, Am J Obstet Gynecol. 1981 Jan;139(1):47-51

Coronary Heart Disease vs. Age



AIHW Heart, stroke and vascular diseases - Australian facts 2004.

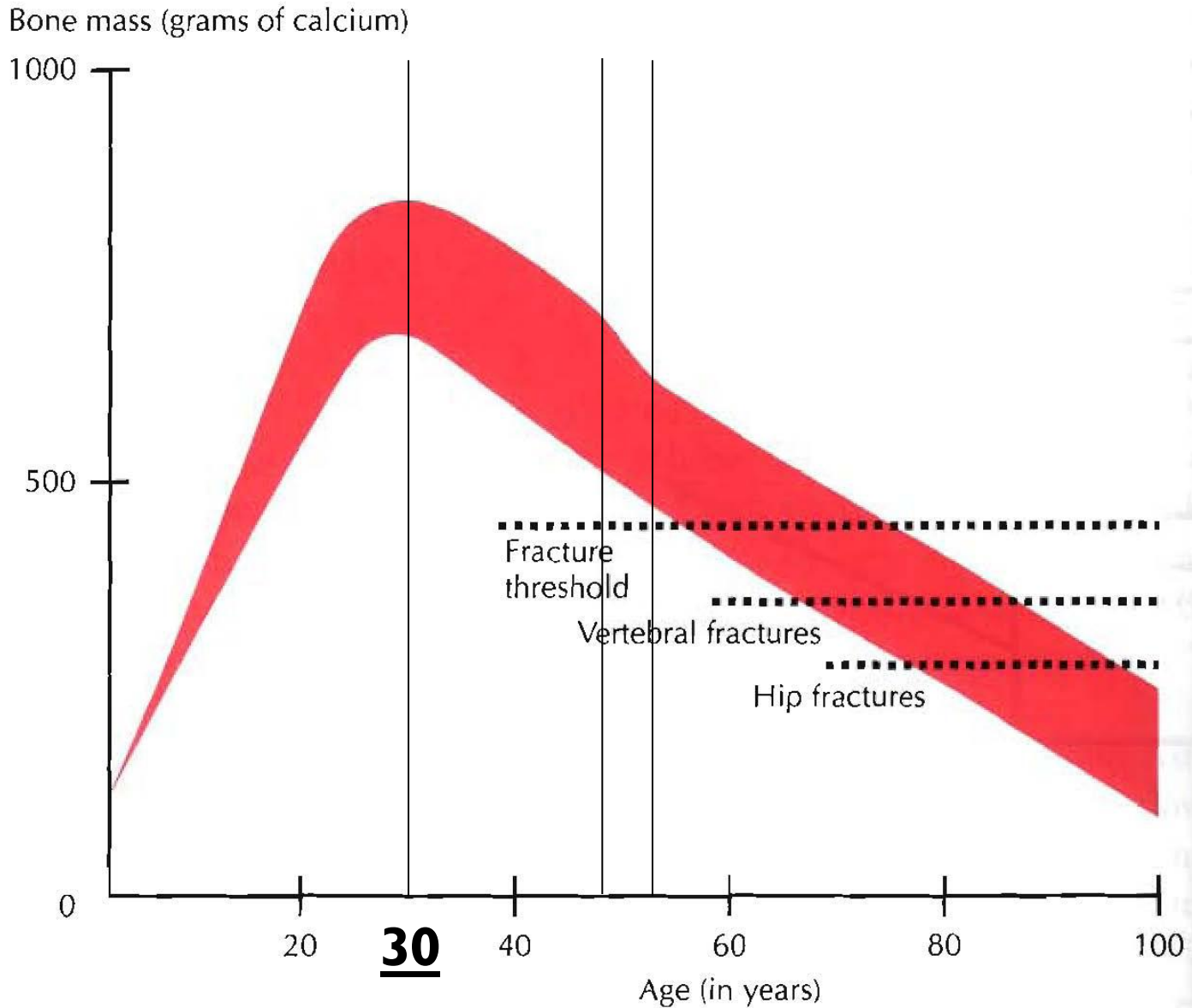
Estradiol vs. Cardiovascular Disease

- ✦ Prevents the oxidation of LDL
- ✦ Improves lipid profile
- ✦ Reduces lipoprotein (a)
- ✦ Reduces blood pressure
- ✦ Improves endothelial function
- ✦ Dilates arteries
- ✦ Reduces plaque formation
- ✦ Improves insulin sensitivity

Estrogen Replacement and CAD

- ✦ Long-term oral Premarin[®] shown to reduce risk of **heart disease** in 40 observational and case-control studies and one randomized study (RR~0.5)
- ✦ Angiographic studies: atherosclerosis ↓'d 50-80%
- ✦ Estrogen reduces plaque size and progression with age
Christian RC, J Clin Endocrinol Metab. 2002 Mar;87(3):1062-7
- ✦ EPAT: rdbpc trial showed less increase in carotid intimal thickness with oral **estradiol** vs. placebo.
Hodis HN, Ann Intern Med. 2001 Dec 4;135(11):939-53
- ✦ But there is a problem with all oral estrogens....

Changes in Women's Bone Mass with Age



Osteoporosis—Impact

- ✦ Menopause: 5% bone loss/year for first 5 years = 25%—due to **loss** of **estradiol**!
 - ✦ 20 yrs. post menopause—**50% reduction** in trabecular bone, 30% in cortical bone
 - ✦ **50% of women** >65 yrs. old have **spinal compression fractures**
 - ✦ **14% lifetime risk of hip fracture** for 50 yr. old woman, **30%** for 80 yr. old.
- Speroff L, Fritz M Clinical Gynecologic Endocrinology and Fertility, 7th Ed.
- ✦ **Bone loss** seen in still-menstruating perimenopausal women with **lower estradiol** and **testosterone** levels.

Steinberg KK, J Clin Endocrinol Metab 1989 Sep;69(3):533-9

Osteoporosis—Prevention and Treatment

✦ **A hormone deficiency** disease—the proper prevention and treatment is **hormone restoration**.

✦ **Estradiol** prevents resorption of old bone while **testosterone, progesterone, DHEA** and **GH** build new bone.

Raisz LG, J Clin Endo Metab. 1996; 81:37-43

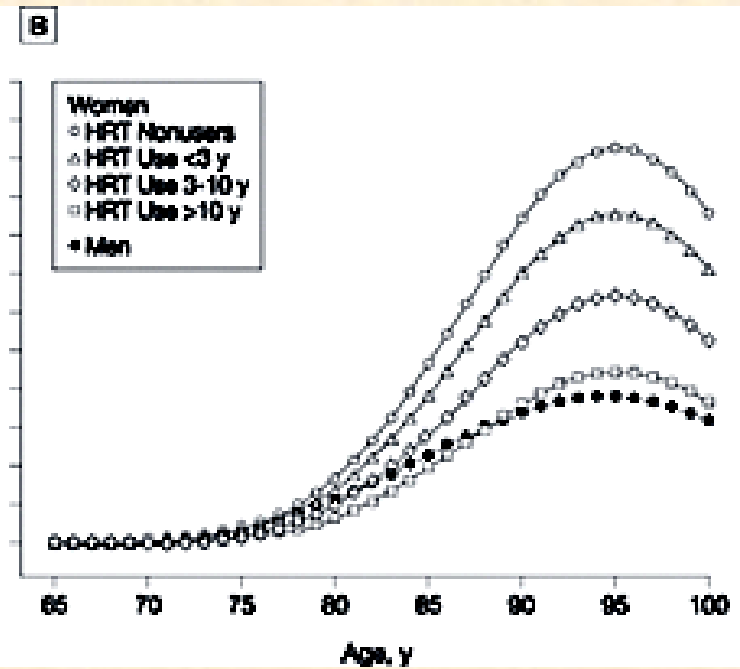
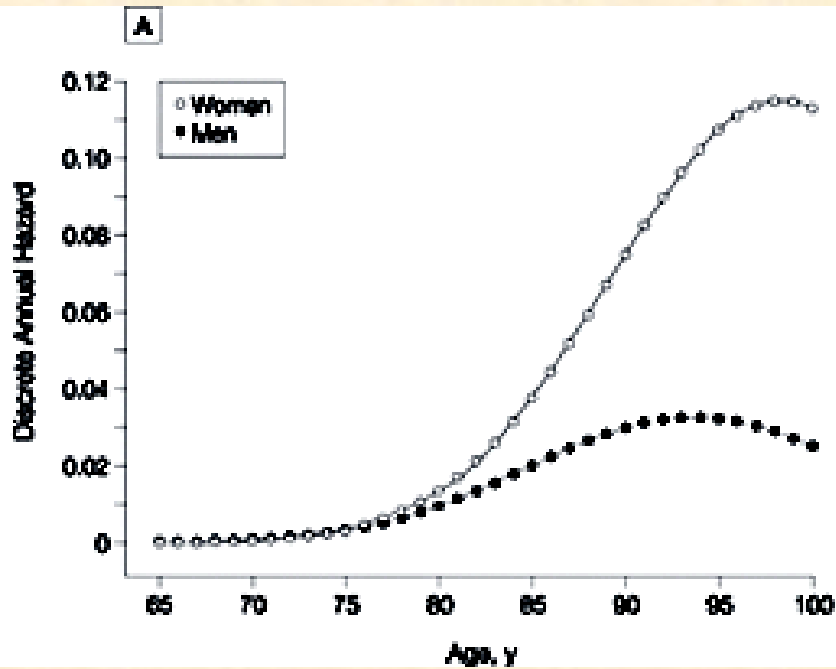
Barrett-Connor E, J Reprod Med. 1999 Dec;44(12):1012-20

✦ **Hormone restoration** increases measured bone density better than biphosphonates **and** preserves normal bone remodeling (no “rotting jaw”, $\downarrow\text{Ca}^{++}$, or suppression of bone formation→poor diaphyseal fracture healing, or late non-traumatic fractures).

✦ Vits. D_3 (a hormone) and K_2 also essential for bone preservation

Iwamoto J, Keio J Med. 2003 Sep;52(3):147-50

Estrogen Replacement Prevents Alzheimer's Disease



72% used Premarin[®] only

Zandi PP, et al., Cache County Study. JAMA. 2002 Nov 6;288(17):2123-9

RR 0.46 in Kawas C, The Baltimore Longitudinal Study of Aging. Neurology 1997;48:1517-1521

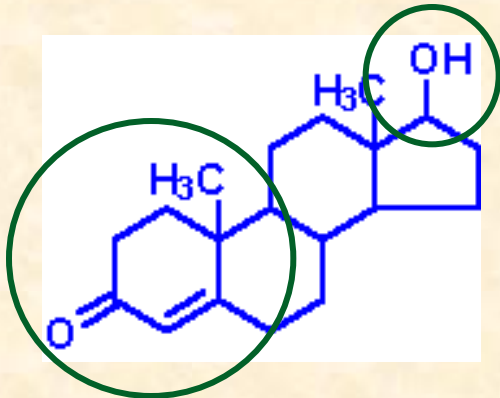
RR 0.65 Paganini-Hill A, Arch Intern Med 1996;156:2213-2217

RR 0.4, Tang M-X, Lancet 1996;348:429-432

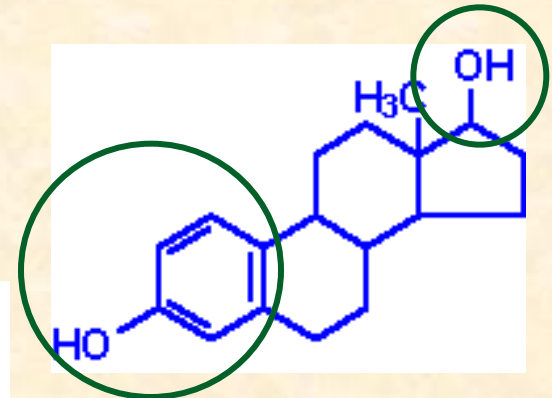
Source of the Confusion:

Hormone Substitution

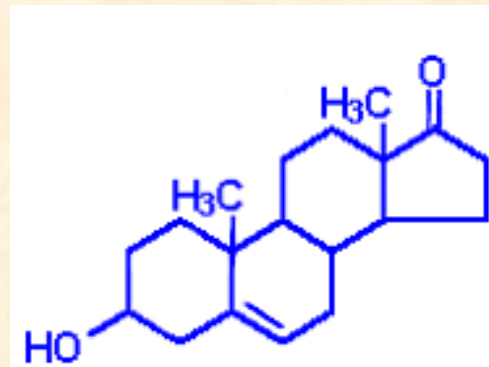
Bioidentical Human Steroid Hormones



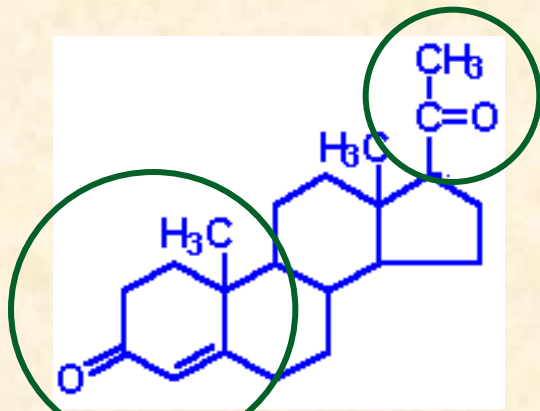
Testosterone



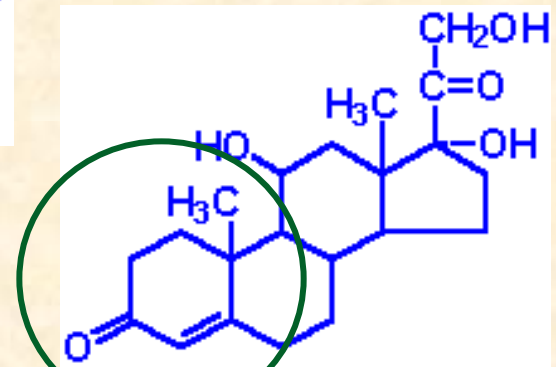
Estradiol



DHEA



Progesterone



Cortisol

Pharmaceutical “Hormone Replacement Therapy”

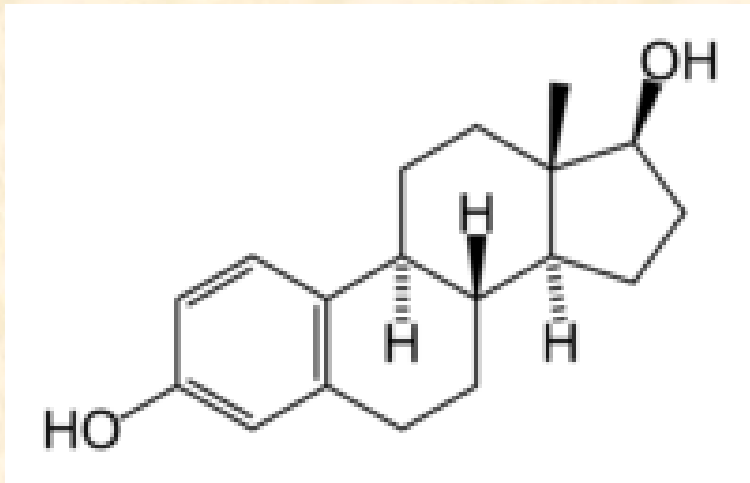
- ✦ Horse-urine **Premarin**® approved in 1942
- ✦ Synthesis of first human steroid hormone, **progesterone**, in 1942. Poorly absorbed orally
- ✦ **Progesterone** altered to make “**progestins**” — among the first **drugs** to be **patented**
- ✦ “HRT” came to mean the use of **alien** molecules that had hormone-like effects.
- ✦ Drug Co.s became dependent on HRT profits.
- ✦ Drug Co.s pushed doctors to use **hormone substitutes** instead of **bioidentical** molecules!

Conventional “HRT” is actually Hormone Substitution Therapy.

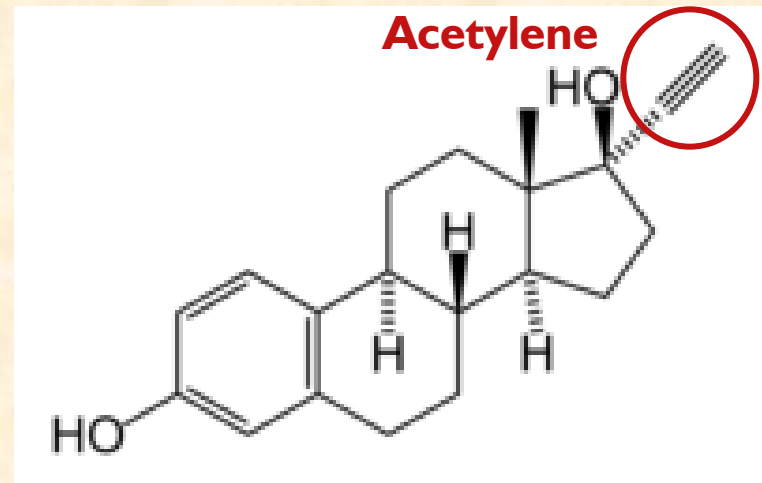
- ✦ **Progesterone substitutes:** medroxyprogesterone acetate (MPA-Provera[®]) and 30+ other “progestins”
- ✦ **Estradiol substitutes:** CEE-Premarin[®] and ethinyl estradiol
- ✦ **Testosterone substitute:** methyltestosterone (metabolizes to super-potent estrogen and ↑’s **breast cancer**)
- ✦ **Patented drugs**—not human **hormones**.
- ✦ **Widespread confusion** due to **misleading** nomenclature: “HRT”, “estrogen”, “progesterone”, and “testosterone” often refer to **substitutes**.

Oral Contraceptives

Estradiol



Ethinyl Estradiol

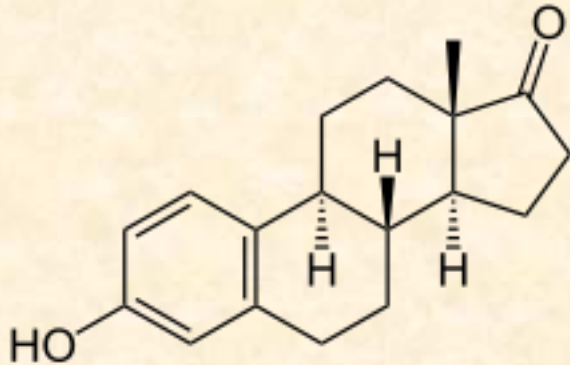


- EE cannot be **inactivated** by normal oxidation.
- EE **does not interact** with estrogen receptor β .
- EE is **12,000-60,000 times more potent** by weight.
- EE is more **thrombogenic** than estradiol.

Premarin[®]

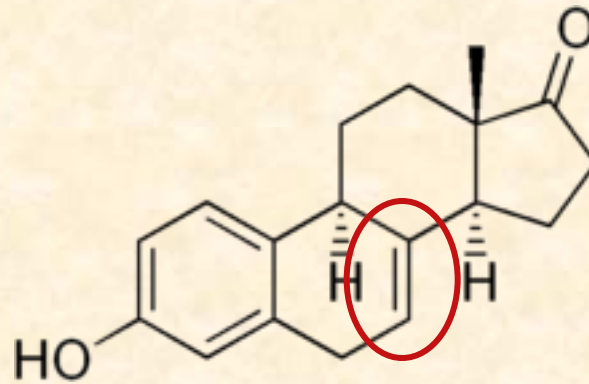
Conjugated Equine Estrogens

Human



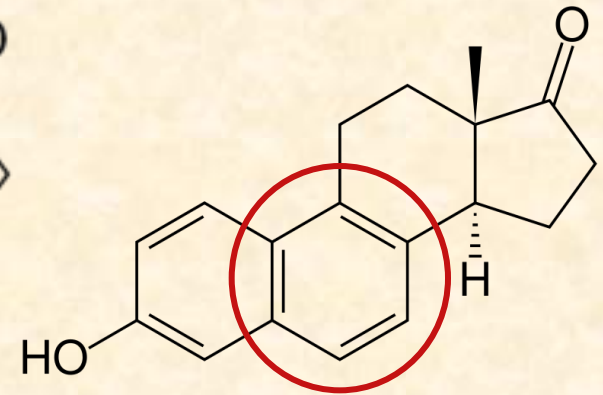
Estrone

Horse



Equilin

Horse



Equilenin

CEE contains at least 10 estrogens, only 3 are human; also contains **horse** androgens and progestins.

Klein R The Composition of Premarin. 1998 Int J Fertil 43:223

Oral Estrogen Replacement is Dangerous

- ✦ First-pass effect on the liver → ↓IGF-1, ↑SHBG, ↑CRP, ↑clotting factors → **blood clots, strokes, heart attacks** in the first year
- ✦ Transdermal **estradiol** has none of these effects!
“Oral but not transdermal estrogen is associated with an increased VTE risk.”
Canonico M, ESTHER study. Circulation. 2007 Feb 20;115(7):840-5
- ✦ Transdermal **estradiol** improves insulin **sensitivity** more than **oral** estrogens.
- ✦ Transdermal **estradiol** provides normal **estrone/estradiol** ratio, while oral **estradiol** is heavily metabolized to estrone by first-pass effect.

CV Risk Factors: Oral ≠ Transdermal Estrogen

Table 7 Effects of oral and transdermal estrogen replacement therapy on the cardiovascular system and various surrogate parameters. The effects may vary according to the type and dose of the estrogens, and may be modulated by the addition of progestogens

<i>Parameter</i>	<i>Oral estrogens</i>	<i>Transdermal estrogens</i>
Risk of thrombosis	increase	possibly smaller increase
Hemostasis	procoagulatory effect	minor effect
APC resistance	increase	minor increase
Atherosclerosis	prevention	prevention
Triglycerides	increase	minor decrease
HDL cholesterol, triglycerides, Apo A	increase	minor increase
LDL cholesterol, remnants, Apo B	reduction	minor reduction
Size of LDL particles	decrease	increase
Activity of metalloproteinases	increase	no effect
Vasodilation	increase	increase
Release of NO, prostacyclin	increase	increase
Release of endothelin-1	reduction	reduction
Angiotensinogen	increase	no effect
C-reactive protein	increase	no effect
Adhesion molecules	decrease	decrease
Cytokines (IL-1, IL-6, TNF- α)	no effect	no effect
PAI-1	decrease	no effect
IGF-1, IGFBP-3	decrease	no effect
IGFBP-1, GH, GHBP	increase	no effect

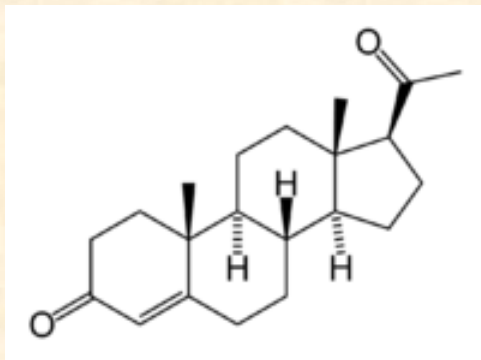
APC, activated protein C; HDL, high density lipoprotein; LDL, low density lipoprotein; Apo, apolipoprotein; NO, nitric oxide; IL, interleukin; TNF, tumor necrosis factor; PAI-1, plasminogen activator inhibitor-1; IGF, insulin-like growth factor; IGFBP; insulin-like growth factor-binding protein; GH, growth hormone; GHBP, growth hormone-binding protein

2002 WHI Study—Premarin®

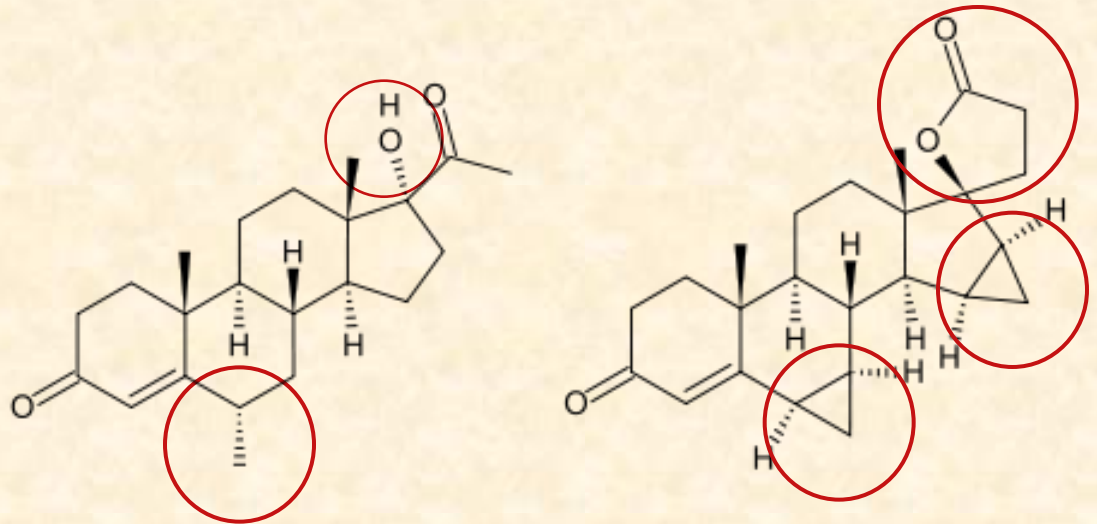
- ✦ Older women (mean age 63), many >20 yrs post menopause
- ✦ Adverse effects in the **first year** (strokes, blood clots), but reductions in CHD afterwards (anti-atherosclerotic effect).
- ✦ No increase risk of **breast CA** (↓IGF-I, ↑SHBG, horse progestins?)
- ✦ Reduced **CHD** and **mortality** in 50-59yr olds, but increased both in 70-79yr olds.
- ✦ Reduced hip fractures by 39%

Progestins \neq Progesterone

Progesterone **Medroxyprogesterone** **Drospirenone**



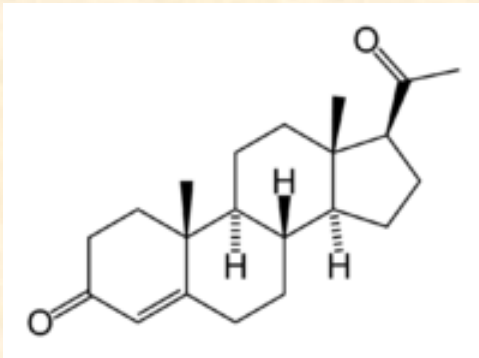
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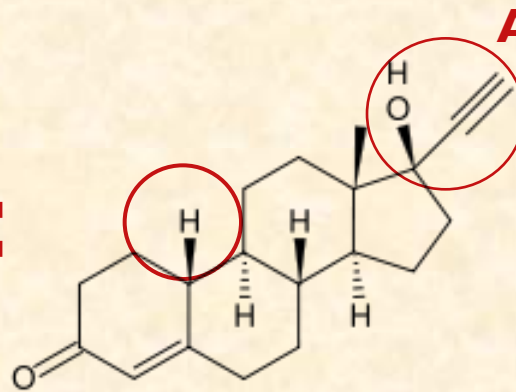
Provera[®] is NOT progesterone.

Progestins \neq Progesterone

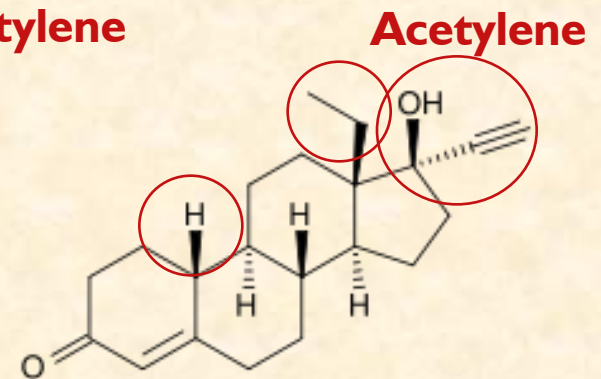
Progesterone



Norethisterone



Levonorgestrel

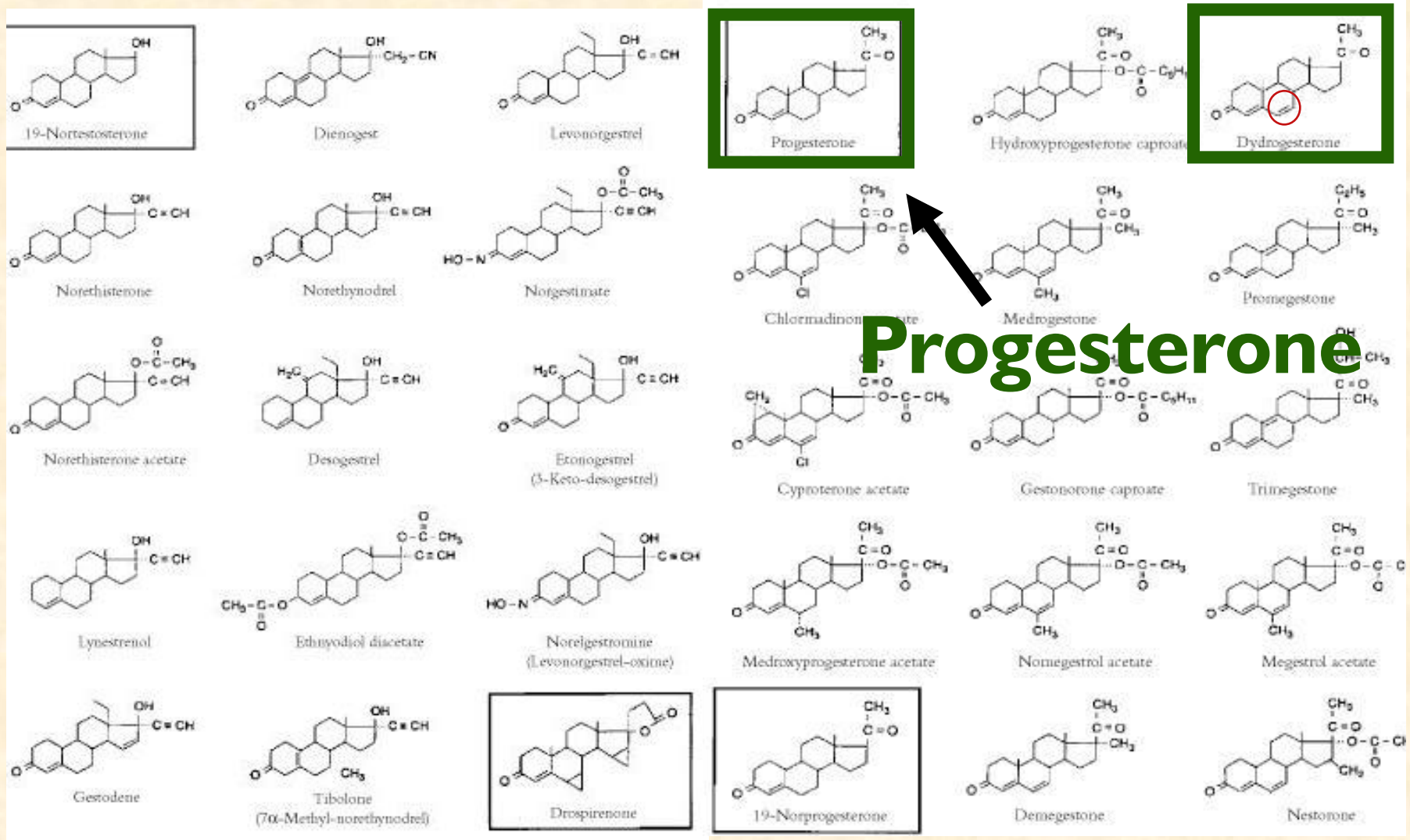


\neq

Progestins are NOT progesterone.

Progestin Zoo

Duphaston®
Most similar



Kuhl, Climacteric 2005;8(Suppl I)

C/w **progesterone**, each **progestin** has a **different spectrum** of androgenic, estrogenic, glucocorticoid, and progestational effects.

Scientific studies show that :

Provera[®] ≠ Progesterone

- Evidence of birth defects
 - Can cause depression
 - Insomnia, irritability
 - Reduces neuroprotection
 - Fluid retention
 - Raises blood sugar
 - Vasoconstriction
 - Increases SM proliferation
 - Increases blood clotting
 - Worsens lipid profile
 - Causes heart attacks
 - Increases MMP activity
 - Increases estrogenic stimulation of breasts
 - **Causes breast cancer**
- Hormone of Pregnancy
 - Improves mood
 - Improves sleep
 - Neuroprotective
 - Diuretic
 - Lowers blood sugar
 - Coronary vasodilation
 - Decreases SM proliferation
 - No increase in clotting
 - Improves lipid profile
 - No evidence of ↑ CVD
 - Reduces MMP activity
 - Reduces estrogenic stimulation of breasts
 - **Prevents breast cancer**

Atherosclerosis and Clotting

*“In both peripheral and cerebral vasculature (of live animals), **synthetic progestins** caused endothelial disruption, accumulation of monocytes in the vessel wall, platelet activation and clot formation, which are **early events in atherosclerosis, inflammation and thrombosis. Natural progesterone or estrogens did not show such toxicity.**”*

Thomas T, Progestins initiate adverse events of menopausal estrogen therapy.
Climacteric. 2003 Dec;6(4):293-301

*“In addition, our data suggest that norpregnane derivatives may be thrombogenic, whereas micronized **progesterone** and pregnane derivatives appear safe with respect to thrombotic risk.”*

Canonico M, ESTHER study. Circulation. 2007 Feb 20;115(7):840-5

WHI Study—Prempro[®]

- ✦ Adding Provera[®] caused more vascular events.
- ✦ CHD RR < 1 for women < 10yrs post menopause, ↑ 1.7 if > 20yrs p.m.
- ✦ Increase in dementia (vascular?, ↓neuroprotection?)
- ✦ Large increase in breast cancer
- ✦ Thousands of lawsuits pending—drug companies running legal-protection propaganda campaign
- ✦ Negative results of WHI DO NOT APPLY to transdermal bioidentical hormones until proven otherwise.

Hormones and Breast Cancer

- ✦ Unopposed estradiol promotes breast cancer.
- ✦ Some progestins also promote breast cancer.
- ✦ Progesterone prevents breast cancer.
- ✦ When estradiol and progesterone are deficient, testosterone and DHEA may ↑ risk.
- ✦ When estradiol is present in youthful quantities, DHEA and testosterone prevent breast cancer.
- ✦ Estradiol restoration is safe if given with progesterone, testosterone, and DHEA to restore the youthful hormonal milieu.

Hormones and Cardiovascular Disease

- ✦ Youthful levels of hormones are **protective**.
- ✦ Both oral and transdermal **estradiol reduce atherosclerosis** in the long term.
- ✦ **Oral**, not transdermal, **estradiol** increases the risk of **thrombi** (DVT, stroke, heart attack).
- ✦ Some **progestins** cause persistent **endothelial inflammation, atherosclerosis, and ↑ clotting**.
- ✦ **Ideal Approach:** Restore **youthful** hormonal milieu with **transdermal bioidentical estradiol, testosterone, progesterone, and DHEA**

Conclusions

- ✦ Women's hormones are not **dangerous**; **the loss** of any or all of their hormones **is dangerous!**
- ✦ Keeping a woman **premenopausal** by restoring **bioidentical** hormones in the **most physiological way** and **in natural balance** must be considered **beneficial** until proven otherwise.
- ✦ Many well-known **benefits**; No proof of **harm**.
- ✦ Since menopausal hormone **deficiencies** are **known** to be **harmful**, those who would **deny** **bioidentical hormone restoration** to women have the **burden of proving** that **harm** > **benefits**.

FDA-Approved Bioidenticals

- ✦ **Estradiol patch (Climara[®], Vivelle[®], etc.)**
- ✦ **Estradiol gel (EstroGel[®])**
- ✦ **Estradiol vaginal ring (Femring[®])**
- ✦ **Progesterone capsules (Prometrium[®])**
- ✦ **Progesterone vaginal gel (Crinone[®])**
- ✦ **Testosterone gel (AndroGel[®])**

Hormone Restoration

- ✦ Unresolved issues—more investigation needed
- ✦ Methods of delivery, dosage, monitoring
- ✦ Need more long-term randomized studies to study long-term results (KRONOS, etc.)
- ✦ Medical profession should be studying **bioidentical hormone restoration** instead of **pharmaceutical hormone substitution!**

For More Information

- ✦ www.hormonerestoration.com
- ✦ Essays on all aspects of hormone restoration
- ✦ Abstracts for all articles quoted can be found under “The Evidence”
- ✦ Contact me:
Henry@hormonerestoration.com

Information Warfare

- ✦ As women switch to pharmacy-compounded **bioidentical hormones**, the **North American Menopause Society (NAMS)** publishes an anti-bioidentical hit piece—confounding bioidentical hormone replacement with questions surrounding compounding and saliva testing:

Boothby L, *Bioidentical hormone therapy: a review* Menopause 2004 Vol. 11, No. 3, pp. 356-367

- ✦ **NAMS** advises that **progesterone AND progestins** both be called “**progestogens**”!
- ✦ NAMS tells women and their doctors: “Use any FDA-approved **progestogen**, but don’t use **natural progesterone** cream”.

NAMS is funded by Pharm. corp’s.

ACOG Caves In to Pressure

October 31, 2005, ACOG NEWS RELEASE No Scientific Evidence Supporting Effectiveness or Safety of Compounded Bioidentical Hormone Therapy

Washington, DC – “There is no scientific evidence to support claims of increased efficacy or safety for individualized **estrogen or progesterone regimens prepared by compounding pharmacies**, ...Furthermore, *hormone therapy does not belong to a class of drugs with an indication for individualized dosing*...ACOG recommends that all of them should be considered to have the same safety issues as those hormone products that are approved by the FDA and may also have additional risks unique to the compounding process.”

(i.e. No differences exist between any: women, estrogens, progestins, **bioidentical** and **alien molecules**, or oral vs. transdermal estrogens. All “hormone” therapies are the SAME!)

ACOG quotes NAMS article repeatedly

ACOG is funded by Pharmaceutical Corporations

Wyeth Piles On

- ✦ October 2005 **Wyeth** (**Prempro**[®]) petitions the FDA to impose restrictions on physicians' ability to prescribe and pharmacists' ability to compound **bioidentical hormones!**
- ✦ Demands same warnings for bioidentical hormone compounds as the FDA requires for Wyeth's **dangerous hormone substitutes**
- ✦ Demands that compounding pharmacies cease promoting **bioidenticals** as more **natural (??)** or **safer (??)** than their **dangerous hormone substitutes!**
- ✦ Motives: Legal protection (**Prempro**[®] lawsuits) and hormone market share

Wyeth/NAMS/ACOG Argument

Hormone-substitution therapy has been proven to be dangerous:

SO

Bioidentical hormone restoration is dangerous too!

Non Sequitur!

The Losers—Women!

Compounded Bioidentical Hormones

- ✦ USP- certified micronized hormones (powder)
- ✦ Standardized compounding practices via PCCA (Professional Compounding Centers of America).
- ✦ Customized delivery system and concentrations
- ✦ Testosterone cream and sublingual progesterone for women not available commercially.
- ✦ Inexpensive—only \$15-40/mo for each hormone.
- ✦ Dosed by clinical effects, serum levels