

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

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This presentation is available on the CD, handout

All “HRT” is not Alike!

- ✦ Menopause is a **hormone-deficiency state** with known **deleterious** consequences for quality of life and health.
- ✦ Estradiol-progesterone-testosterone (EPT) replacement for menopause is medically necessary.
- ✦ Estradiol replacement is safe when transdermal and accompanied by sufficient **progesterone** and **testosterone**.
- ✦ **Bioidentical EPT** therapy does not have the **cardiovascular** or **breast cancer risks** seen with **PremPro®**.
- ✦ How to provide **EPT** therapy to menopausal women

Hormones are not Drugs

- ✦ Vital parts of our neuro-endocrine-immune system
- ✦ Proper **fit** in all receptors, normal metabolism-elimination
- ✦ Non-toxic, **inherently safe**
- ✦ No allergic or idiosyncratic reactions
- ✦ No side effects, only effects!
- ✦ Can monitor therapy with the usual blood tests
- ✦ The only problems that can occur with **bioidentical hormones**:
 - ◆ **Excessive** or insufficient dose
 - ◆ Lack of **balance** with other hormones
 - ◆ **Unphysiological** delivery: route, timing, etc.
 - ◆ Exacerbation of some underlying disease

Not Just “Sex Hormones”

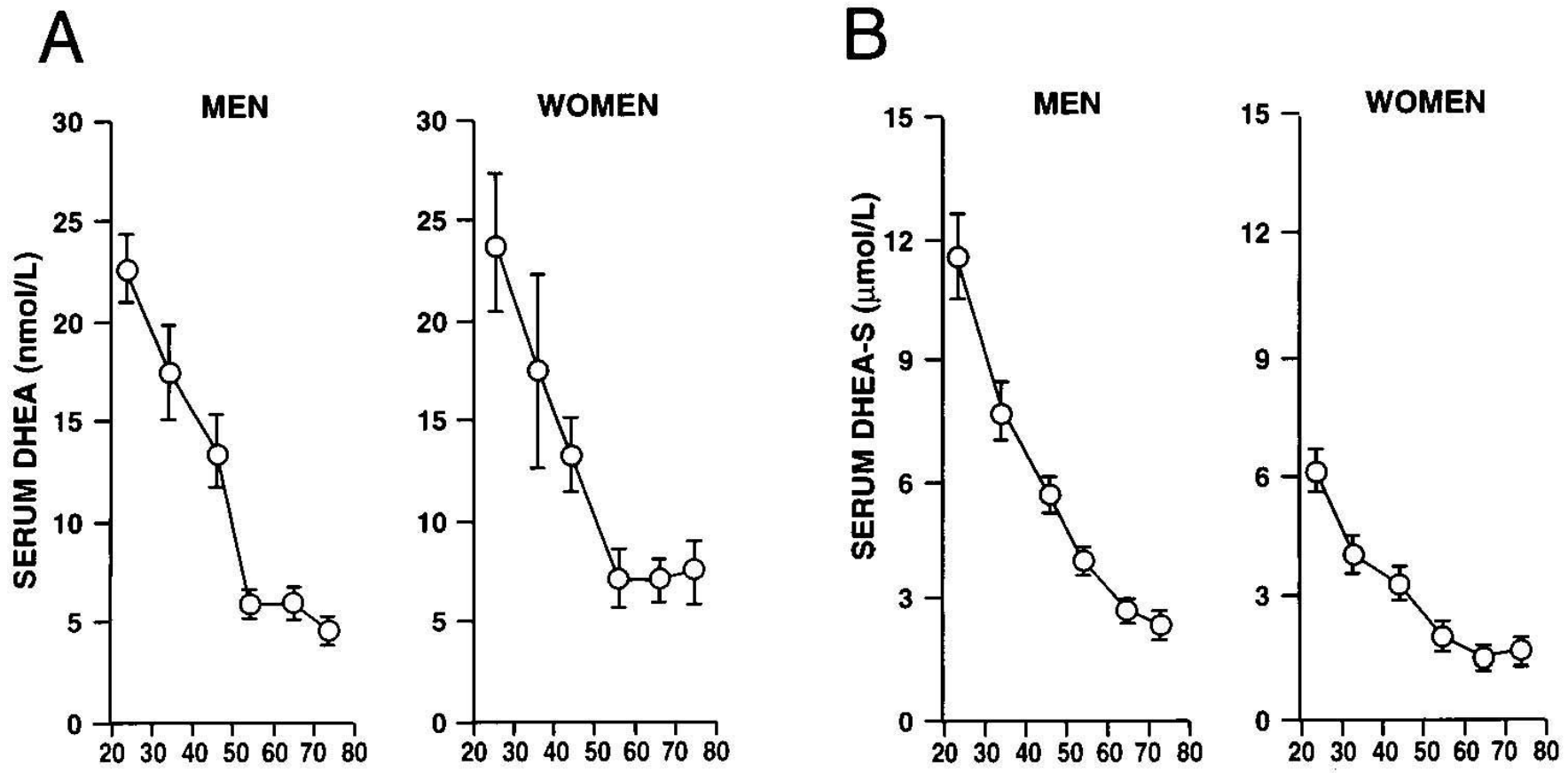
- ✦ Estradiol, progesterone, and testosterone are required for the growth, function and maintenance of all tissues in both sexes!
 - ◆ Maintain brain function and health—vital neurosteroids
 - ◆ Maintain tissue health/strength: skin, hair, bone, muscle, heart
 - ◆ Improve insulin sensitivity: ↓ belly fat, ↓ risk of diabetes
 - ◆ Reduce blood pressure: improve endothelial function
 - ◆ Prevent atherosclerosis: reduce risk of MI, stroke

What about the loss of hormones with **aging**?

Adrenopause

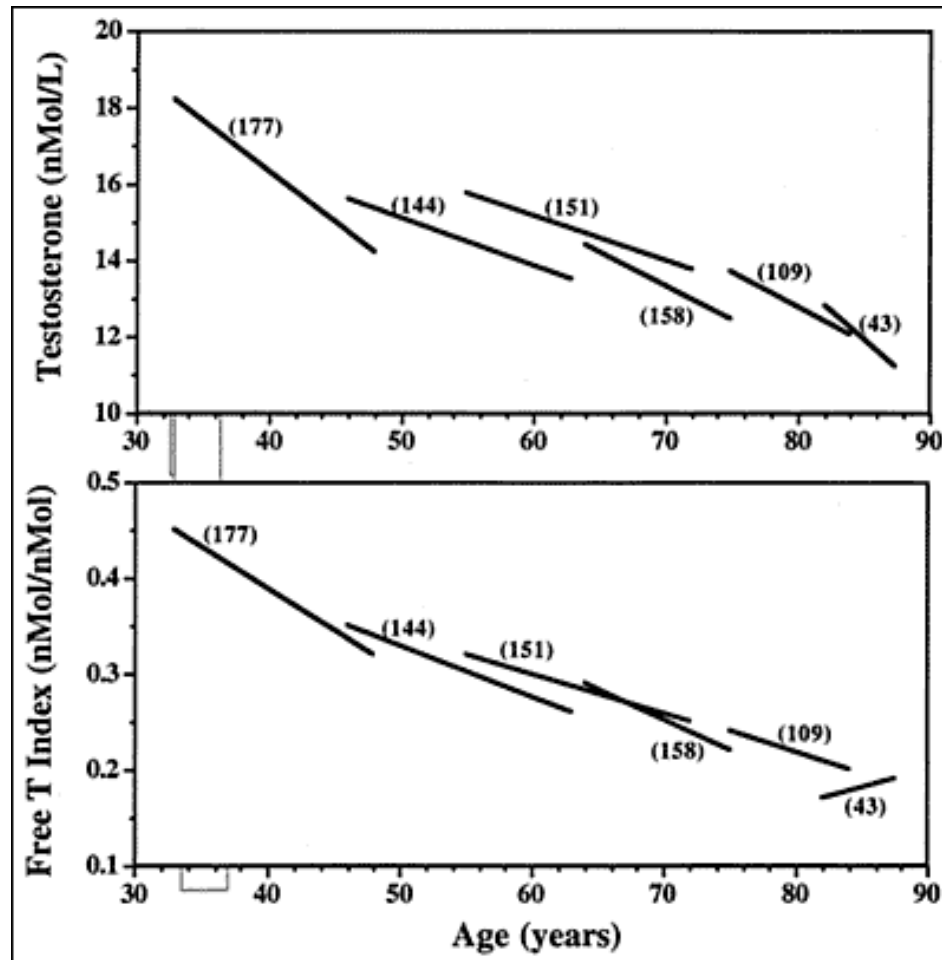
DHEA ↔ DHEA-S

Converted into estradiol and testosterone within tissues



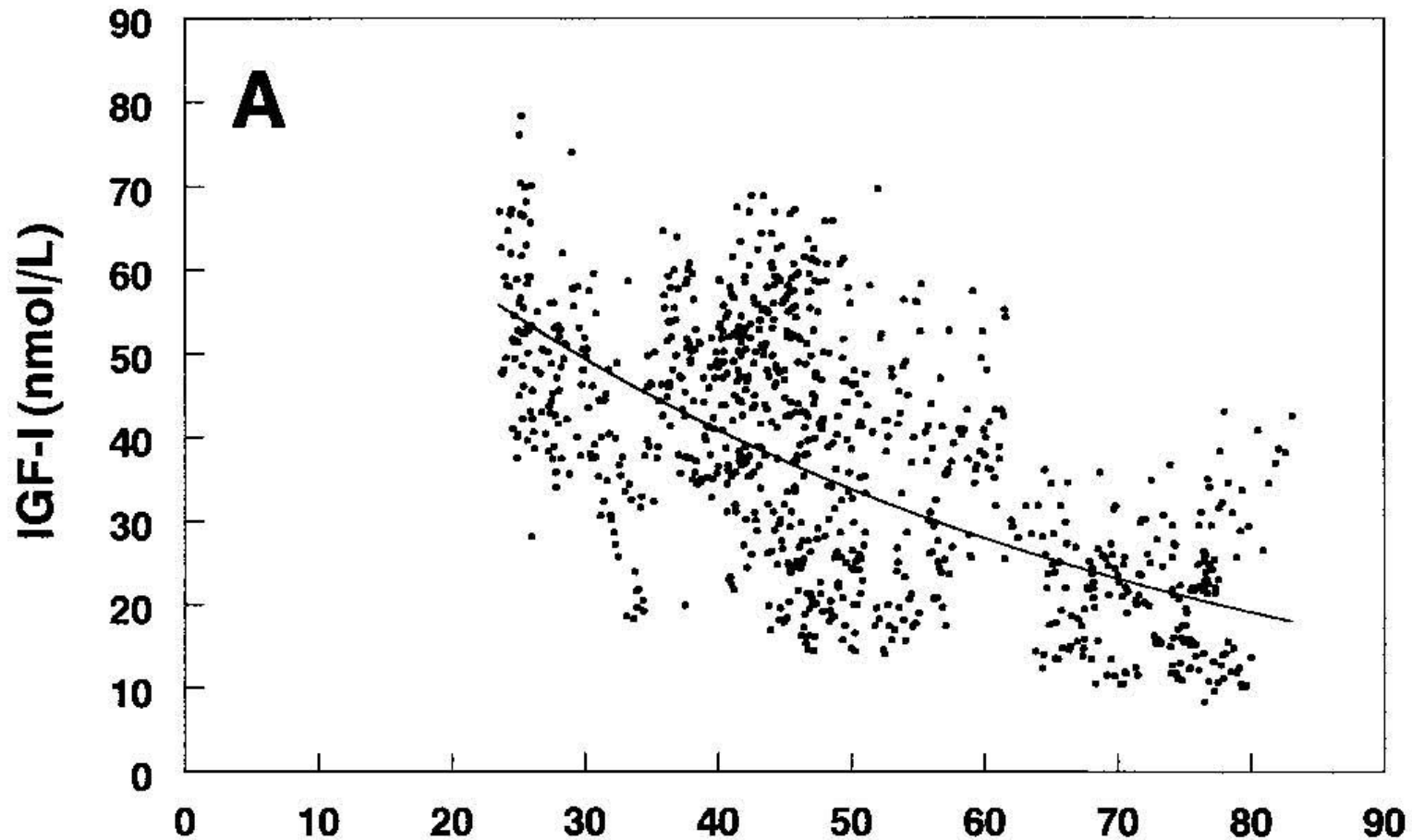
Andropause

Testosterone in Men



Somatopause

Growth Hormone



Thyropause

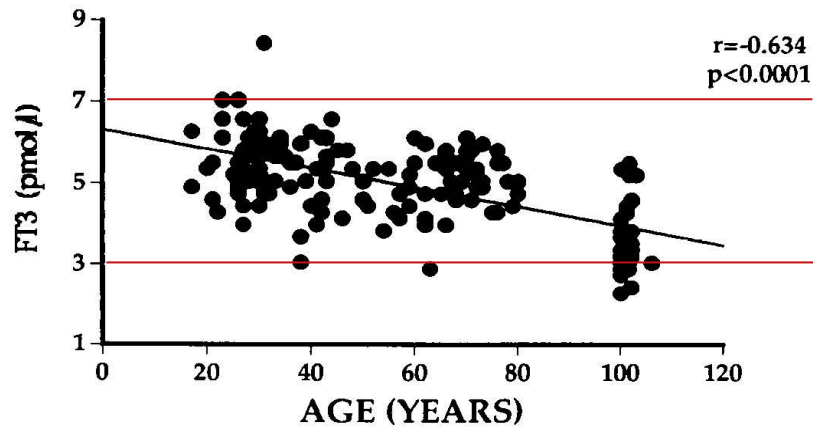


FIG. 7. Age-dependent variations in serum FT₃ concentration in healthy human subjects up to centenarians [Modified from S. Mariotti *et al.*: *J Clin Endocrinol Metab* 77:1130–1134, 1993 (147), with publisher's permission. © The Endocrine Society.]

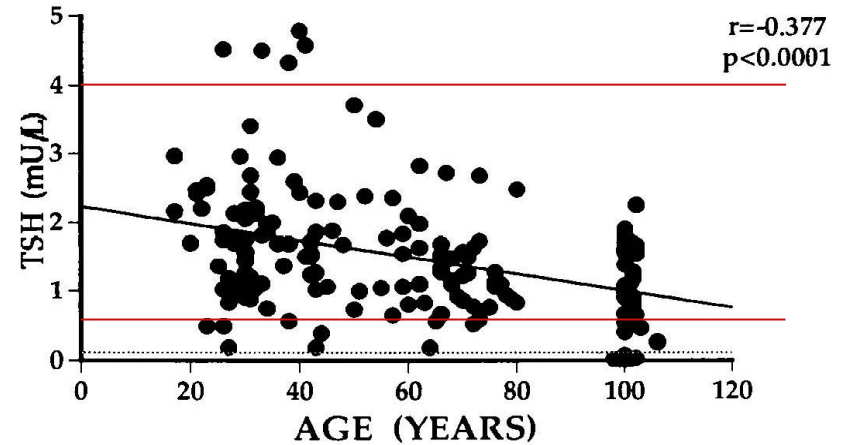
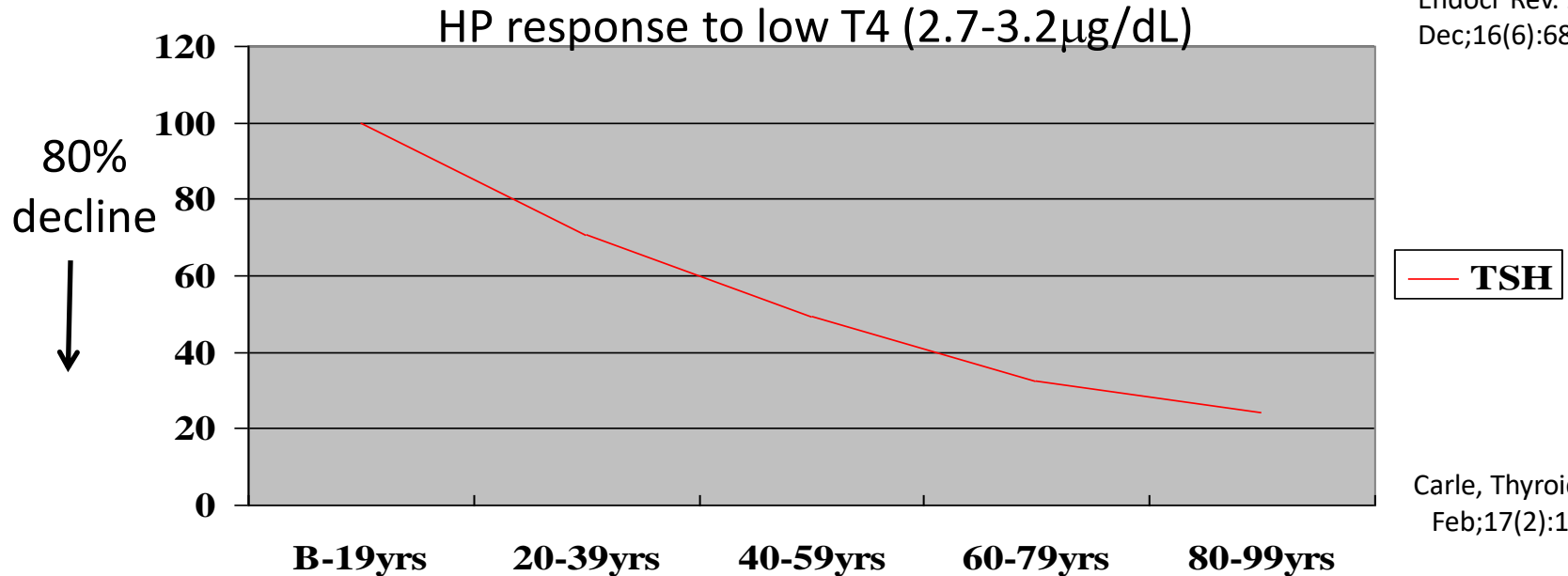


FIG. 8. Age-dependent variations in serum TSH concentration in healthy human subjects up to centenarians [Modified from S. Mariotti *et al.*: *J Clin Endocrinol Metab* 77:1130–1134, 1993 (147), with publisher's permission. © The Endocrine Society.]

Endocr Rev. 1995
Dec;16(6):686-715



Carle, Thyroid. 2007
Feb;17(2):139-44

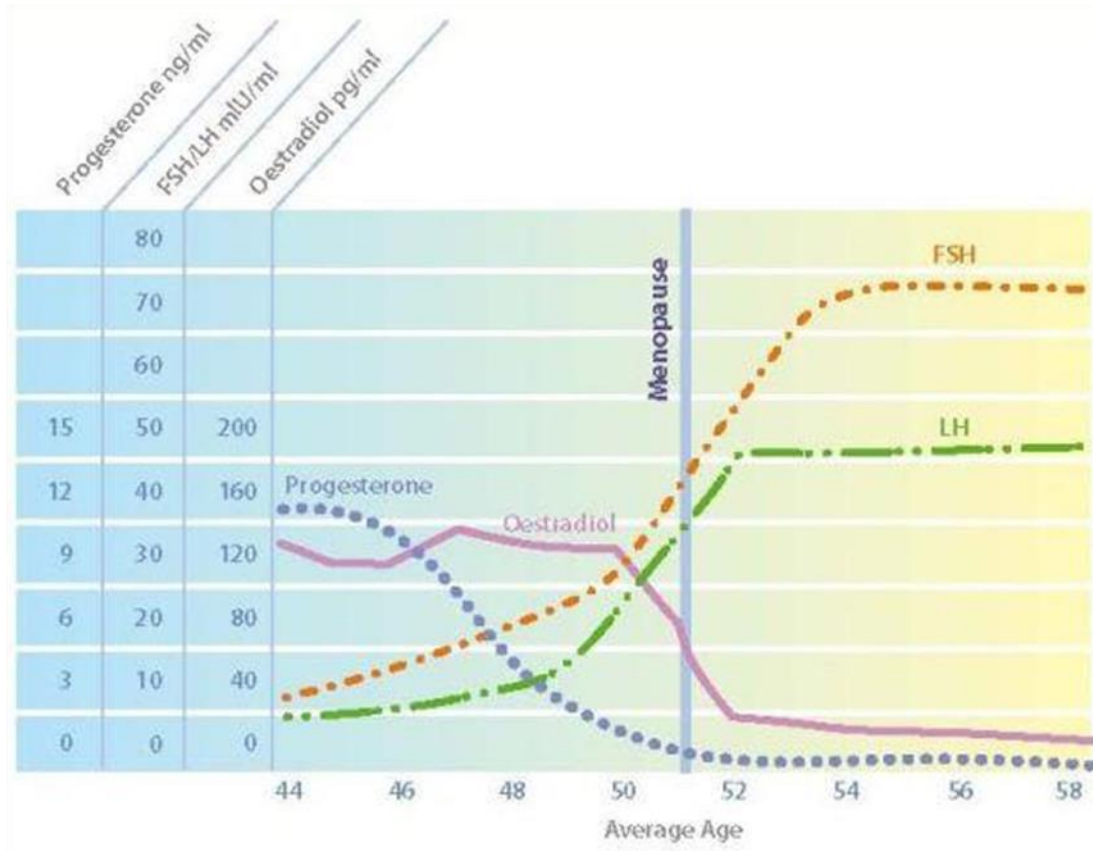
Hormone Loss with Age

- ✦ Common Assumption: Hormone loss with age is adaptive. Youthful hormone levels would cause **heart attacks** and **cancer** later in life;
- ✦ But: **Heart attacks**, **osteoporosis** and sex-organ **cancers** occur years after hormones decline and in persons with lower hormone levels.
- ✦ Fact: **Aging** is not adaptive: it is pre-programmed **Dying**—to remove individuals from the gene pool and permit evolution.
- ✦ Hormone **loss** is caused by and contributes to **aging**.
- ✦ The **loss** of hormones with age is both natural and **deleterious**.
- ✦ **Nature is Trying to Kill Us!**

Menopause is Endocrine Gland Failure

- ✦ The ovaries produce estradiol, progesterone and testosterone.
- ✦ Gradual loss of egg follicles with aging.
- ✦ The ovaries are the only endocrine glands that fail completely in all persons
- ✦ FSH remains high for life—the brain doesn't consider menopause to be “normal” or good!
- ✦ The menopausal endocrinopathy is both natural and deleterious.

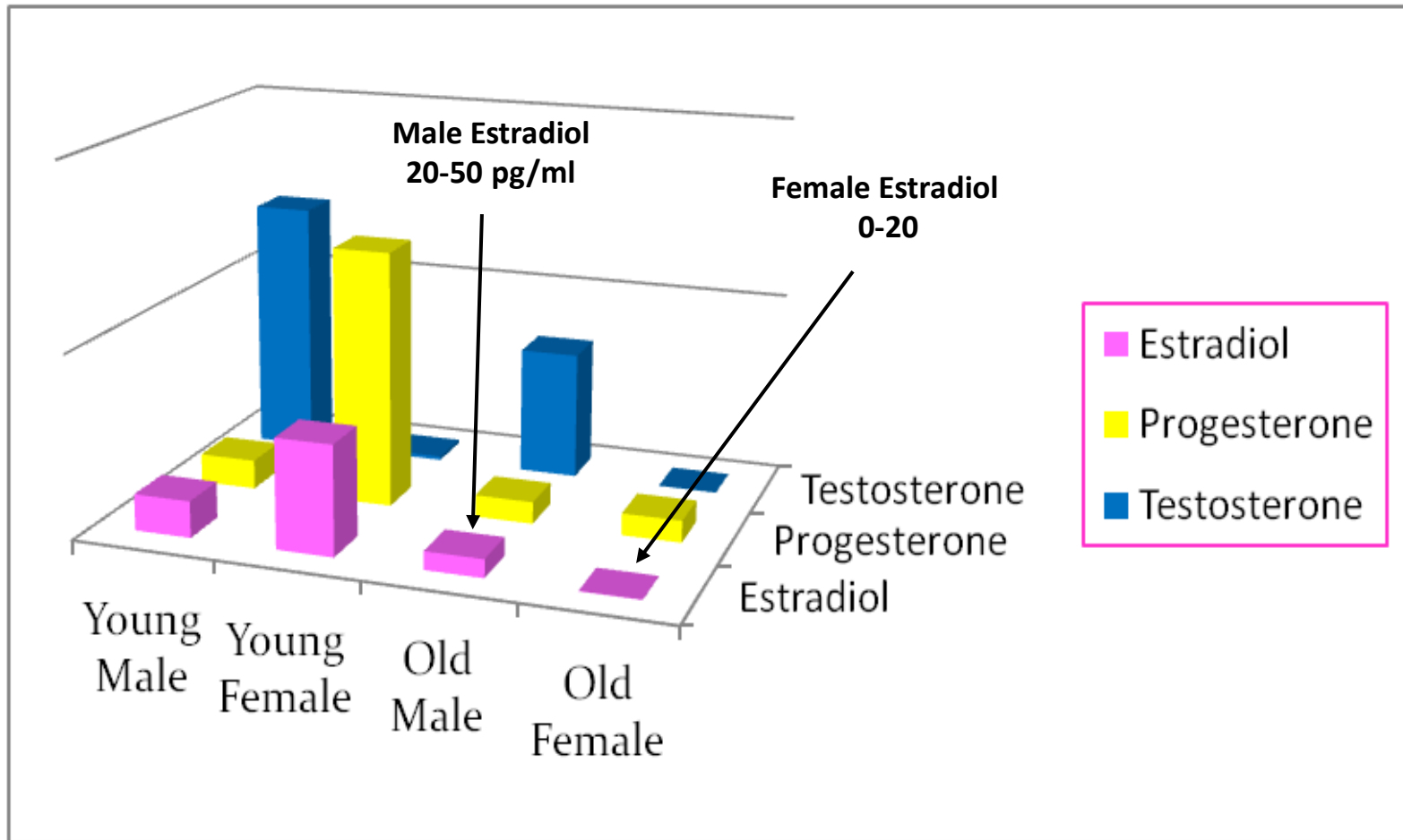
Menopause



The decline estradiol and progesterone in perimenopause along with the rise in LH and FSH.

No longer found at [original site](#).

Menopause



Estradiol Deficiency

- ✦ Hot flashes, night sweats
- ✦ Insomnia, depression, fatigue, achiness
- ✦ **Mental** deterioration: poor memory recall, ↑'d risk of **dementia**
- ✦ **Urogenital atrophy**: vaginal dryness, incontinence
- ✦ **Atrophy** of **bone**, **skin**, and connective tissue
- ✦ Endothelial **dysfunction**, ↑'d blood pressure
- ✦ **Atherosclerosis**, heart disease
- ✦ Insulin **resistance**-- ↑'d risk of **diabetes**

The symptoms of menopause are **warning signs** of physical and mental **deterioration**.

Progesterone Deficiency

- ✦ Progesterone counteracts estradiol in the breasts and uterus
- ✦ **Estrogen dominance** → heavy menses, breast tenderness, fluid retention, moodiness.
- ✦ Overstimulation of **breast** and **uterine** epithelia ↑'d risk of breast and uterine **cancers**.
- ✦ Progesterone production declines as early as age 30 → luteal phase insufficiency = **estrogen dominance**.
- ✦ Perimenopause — **anovulation**; little-to-no progesterone production for years.
- ✦ The treatment for perimenopausal **estrogen dominance** is **progesterone**, not hysterectomy

Testosterone Deficiency

- ✦ Female testosterone levels are 1/20th those of men
- ✦ Female testosterone drops 50% between age 20 and 40.
Zumoff B, J Clin Endocrinol Metab. 1995 Apr;80(4):1429-30
- ✦ 50% of serum testosterone in females comes from DHEAS.
- ✦ Oral estradiol HRT → ↓total testosterone 42%, ↓DHEAS 23%
Casson PR, Obstet Gynecol.1997 Dec;90(6):995-8
- ✦ Birth control pills → ↓free testosterone 60%, ↓DHEAS 30%
White T, Am J Obstet Gynecol. 2005 Jun;192(6):2055-9

Testosterone Restoration

- ✦ Improves energy, mood, well-being

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

- ✦ Reduces fearfulness, anxiety

- ✦ Improves sexual desire and sensation

- ✦ Improves muscle strength and recovery

- ✦ Improves insulin sensitivity

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

- ✦ With **estradiol**, increases in bone density

Davis SR, Maturitas 1995; 21:227-236
Menopause. 2000 Sep-Oct;7(5):318-26

Miller BE,

- ✦ Improves flow-mediated arterial dilation

- ✦ May **decrease** 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

- ✦ Anti-proliferative effect in breast; **reduces** risk of **breast cancer**

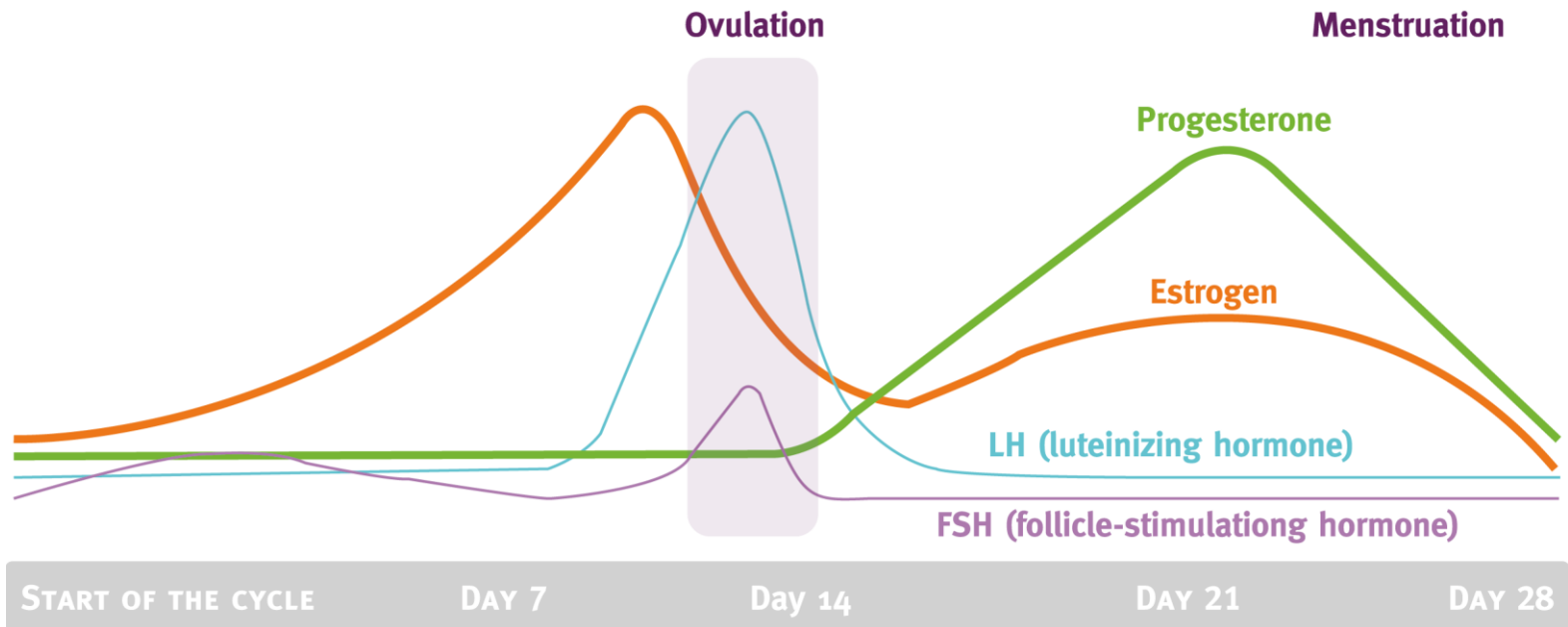
Women Killers and Hormones

- ✦ Breast cancer, cardiovascular disease (CVD), and osteoporosis are all rare before menopause.
- ✦ All three diseases are related to aging and to sex-steroid deficiencies or imbalances.
- ✦ The youthful estradiol-progesterone-testosterone hormonal milieu protects women from these diseases.

Reproduction and Sex-Organ Cancers

- ✦ The complex female endocrine system is an evolutionary compromise; to produce and feed babies.
- ✦ Reproduction has costs: poses **threats** to female health and quality of life.
- ✦ 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**.

Menstrual Cycle



Historical Perspective

- ✦ Throughout history, women were usually pregnant or breast feeding; both **protective** against **breast cancer**.
- ✦ They had only 4 years of cycling on average.
- ✦ Today, women may experience 35 years of cycling →
- ✦ ↑'d risk of **breast, ovarian** and **uterine cancers** and other diseases and disorders (**PCOS, PMS, endometriosis, ovarian cysts, etc.**).

Estradiol and Cancer

- ✦ Cancers are caused by genetic **mutations**; not sex hormones
- ✦ **Estradiol** stimulates cellular **proliferation** in the breasts and uterus.
- ✦ **Progesterone** and **testosterone** oppose estradiol's stimulatory effects in the breasts.
- ✦ **Unopposed estradiol** and some **progestins** facilitate **cancer** growth, thereby increasing tumor detection in short-term studies.

Estradiol-Progesterone Complementarity

- ✦ Estradiol promotes **proliferation** in uterus and breasts.
- ✦ Progesterone stops proliferation and promotes **maturation** and **differentiation** in the uterus and breasts.
- ✦ Progesterone withdrawal → sloughing and necrosis of uterine lining and breast duct epithelium.
Longacre TA, Am J Surg Pathol. 1986 Jun;10(6):382-93
- ✦ A high persistent **progesterone/estradiol** ratio suppresses **proliferation** and prevents uterine and breast **cancers**.

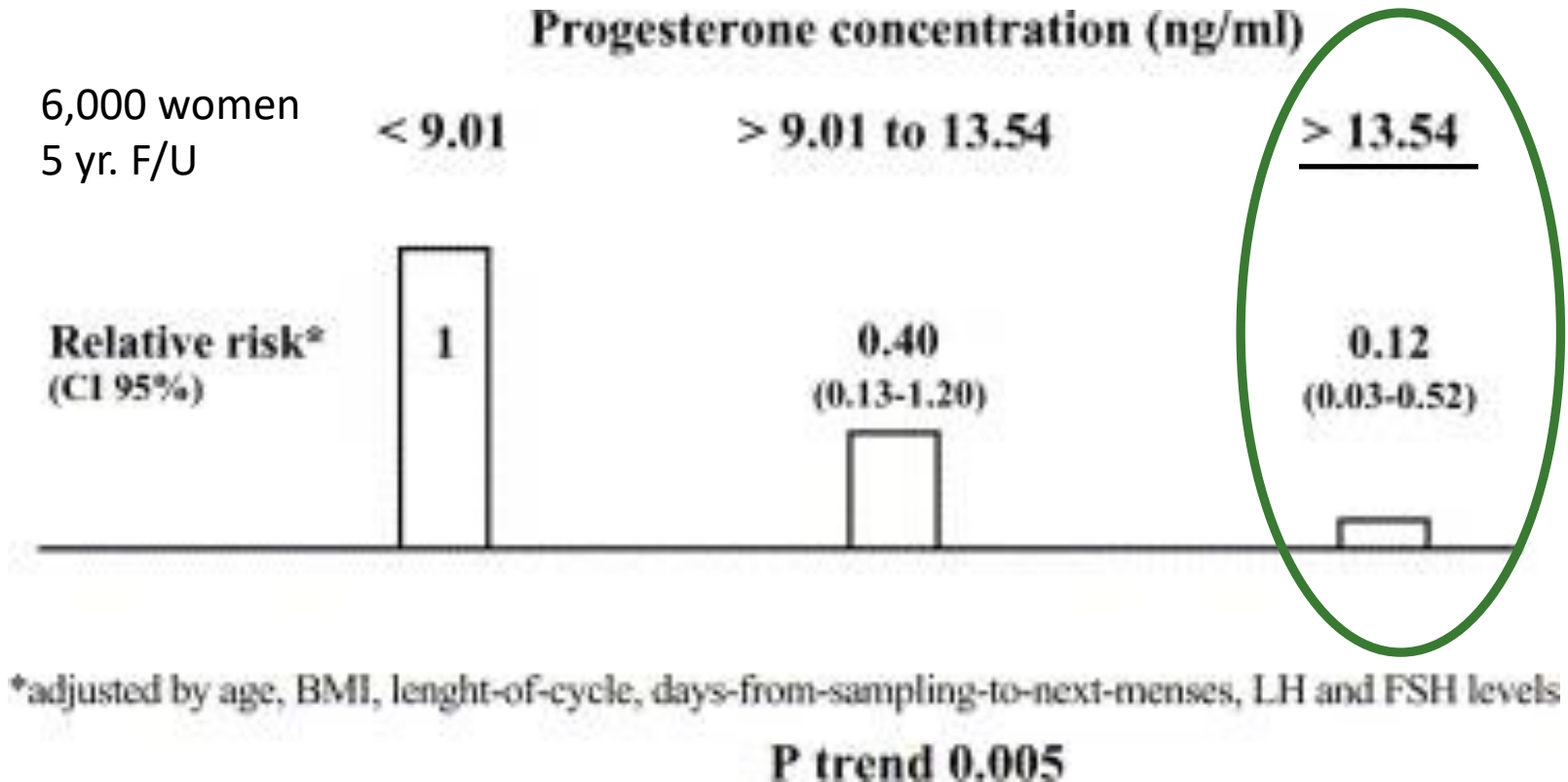
Progesterone's Anti-Estrogenic Actions in Uterus and Breast

- ✦ Decreases synthesis of estradiol receptors
- ✦ Increases conversion of estradiol to inactive estrone by inducing 17 β -hydroxysteroid dehydrogenase 2
- ✦ Reduces conversion of inactive estrone to estradiol by inhibiting 17 β -hydroxysteroid dehydrogenase 1
- ✦ Increases sulfation (inactivation) of estrogens
- ✦ Inhibits binding of estradiol to receptors
- ✦ Inhibits production of estradiol by aromatization

Progesterone Deficiency/Resistance → Breast Cancer

- ✦ Premenopausal women with **low progesterone** levels have **5x risk** of early **breast cancer**
Cowan LD, Am J Epidemiol 1981;114:209-17
- ✦ Many **breast cancer** victims have **progesterone resistance**.
Simpson HW, Br J Obstet Gynaecol. 1998 Mar;105(3):345-51
- ✦ BRCA1 and 2 carriers have **progesterone resistance**.
Ma Y et al. Mol Endocrinol. 2006 Jan;20(1):14-34
Guo YX et al. Nan Fang Yi Ke Da Xue Xue Bao. 2008 Jul;28(7):1157-60
- ✦ **Progesterone** reduces estradiol-induced growth of ER+/PR+ breast cancer tumors.
Mohammed H et al. Nature. 2015 Jul 16;523(7560):313-7
- ✦ **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

High Luteal Progesterone Prevents Breast Cancer



Micheli A, Ordet Study: Int. J. Cancer **112** (2004) (2), pp. 312-318.

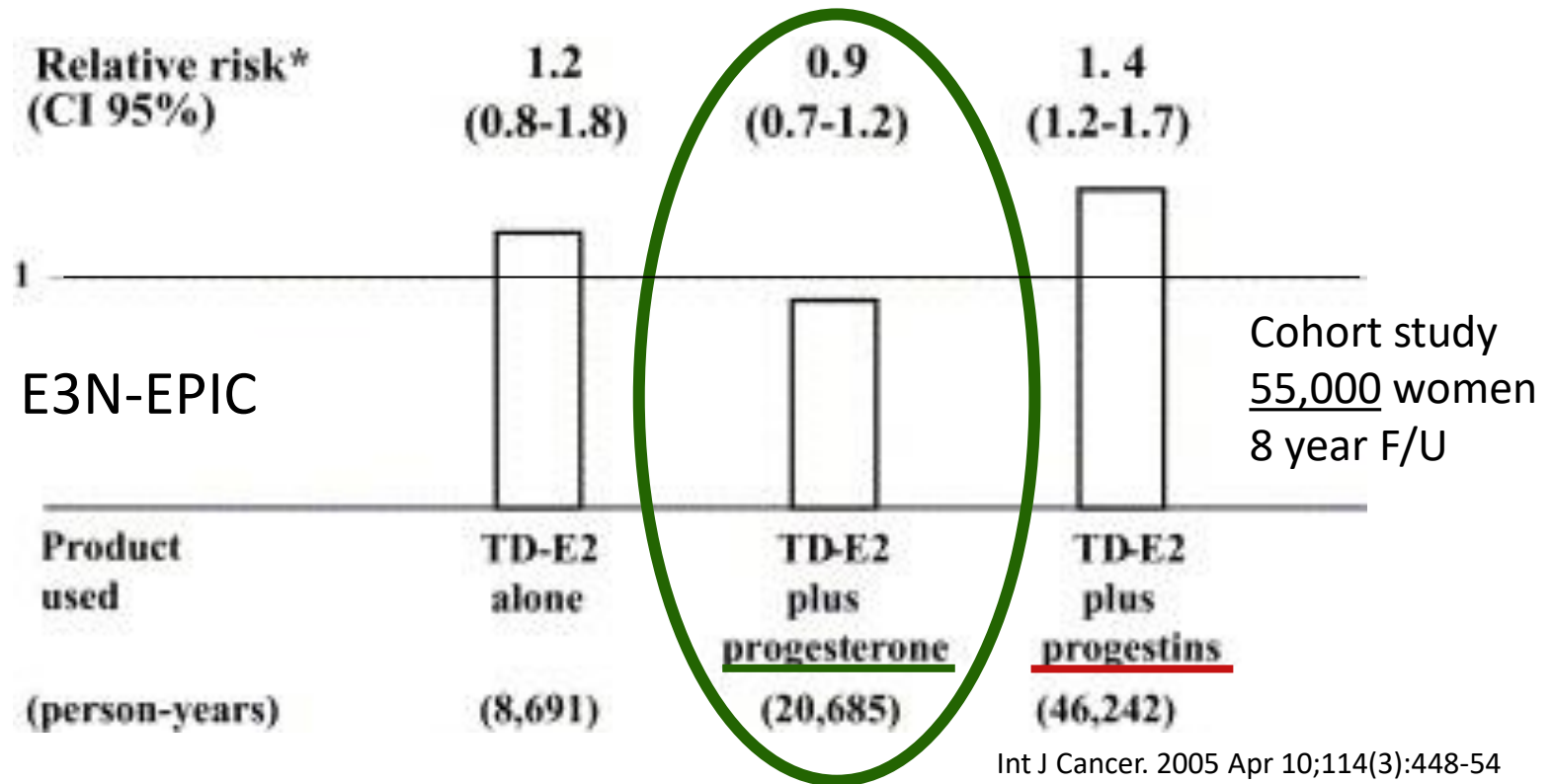
See also: Sturgeon SR Cancer Causes Control. 2004 Feb;15(1):45-53.

Progesterone vs. Breast Cancer

- ✦ Progesterone cream applied to the breasts **reduces** proliferation.
Chang KJ, Fertil Steril 1995; 63:785-91
Barrat J, J Gynecol Obstet Biol Reprod (Paris). 1990;19(3):269-74
- ✦ Breast cells proliferate with 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
- ✦ Estradiol promotes **cancers** in breast cell cultures unless progesterone is present.
Russo J, J Steroid Biochem Mol Biol. 2003 Oct;87(1):1-25
- ✦ Estradiol upregulates **cancer-promoter** gene bcl-2, progesterone downregulates it.
Formby B, Ann Clin Lab Sci. 1998 Nov-Dec;28(6):360-9
- ✦ 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

EP Studies: No ↑ in Breast Cancer

TD-E2=transdermal estradiol; progesterone=100mg oral capsule



De Lignieres B et al. Combined hormone replacement therapy and risk of breast cancer in a French cohort study of 3175 women. *Climacteric* 2002;5:332-40.

Cordina-Duverger E et al. Risk of breast cancer by type of menopausal hormone therapy: a case-control study among post-menopausal women in France. *PLoS One*. 2013 Nov 1;8(11):e78016.

Espié M et al. Breast cancer incidence and hormone replacement therapy: results from the MISSION study, prospective phase. *Gynecol Endocrinol*. 2007 Jul;23(7):391-7.

The Europeans Get It

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

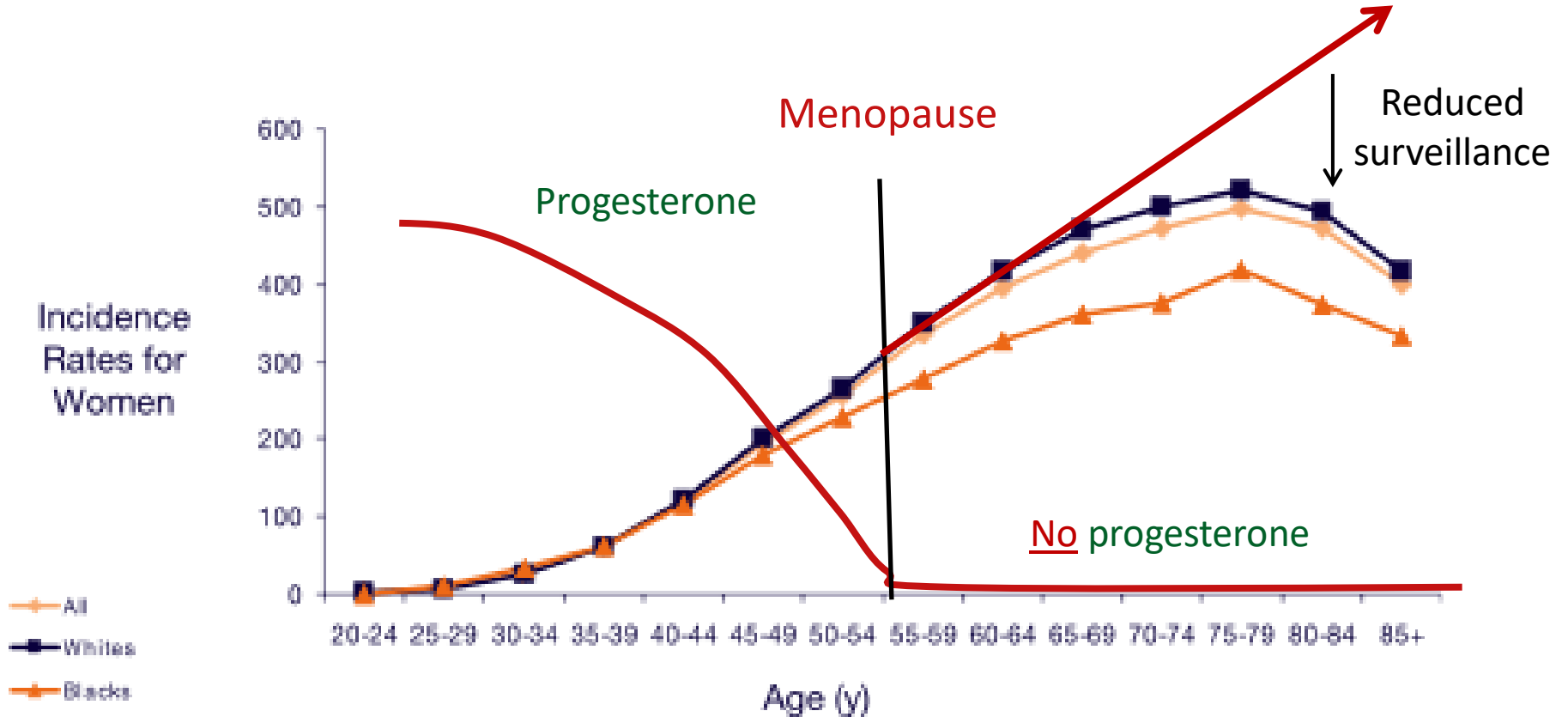
Campagnoli C. Progestins and progesterone in hormone replacement therapy and the risk of breast cancer. J Steroid Biochem Mol Biol. 2005 Jul;96(2):95-108.

*“The hypothesis of **progesterone**...decreasing the proliferative effect of estradiol in the postmenopausal breast remains highly plausible and (**progesterone**) should be...the first choice for symptomatic postmenopausal women.”*

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

Breast Cancer Rate vs. Age

Loss of progesterone → higher risk of breast cancer



The Key: Intramammary Steroids

- ✦ Breasts produce **estradiol** locally from adrenal androgens (**DHEA**, **androstenedione**)
 - ✦ Compared to the premenopausal breast, postmenopausal breast nipple aspirate fluid has:
 - ◆ Same estradiol concentration (~youthful serum conc.)
 - ◆ Much lower **progesterone** concentration
- Chatterton RT Clin Endocrinol Metab. 2005 Mar;90(3):1686-91
- ✦ Breasts get **progesterone** from the blood, concentrate it by 3-4x.
- Gann PH, Cancer Epidemiol Biomarkers Prev. 2006 Jan;15(1):39-44
- ✦ No **progesterone** → intramammary **estrogen dominance** → **breast cancer**.

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

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

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

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

Dimitrakakis C, Menopause. 2004 Sep-Oct;11(5):531-5 (508 women; 8 yrs.)

- ✦ Testosterone in F→M transsexuals →involution of breast tissue

Slagter MH, J Histochem Cytochem. 2006 Aug;54(8):905-10

- ✦ Testosterone is an effective treatment for breast cancer.

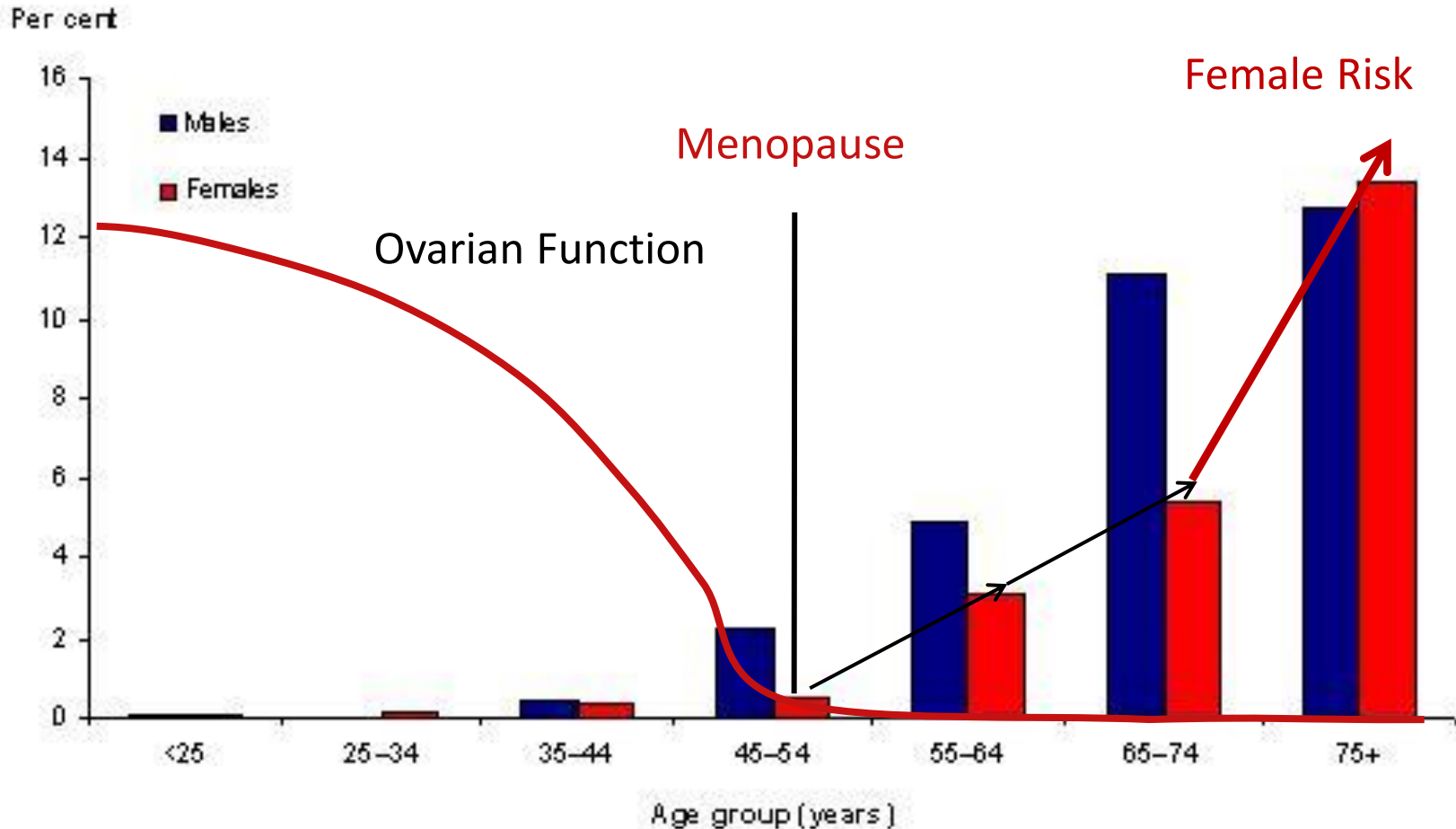
Labrie F, Cancer Detect Prev. 1992;16(1):31-8 (review)

Confusion about Androgens in Women

- ✦ Some studies show increased **breast cancer** and **cardiovascular disease** in premenopausal women with higher **testosterone** levels.
- ✦ Confounder—PCOS: Higher premenopausal **testosterone** levels are caused by polycystic ovarian syndrome with **high insulin** and **low progesterone** levels.
- ✦ Postmenopause: **DHEA** and **testosterone** can be converted into estradiol within the breasts, at some levels may increase risk of **breast cancer** in the absence of **progesterone**.

Don't estrogen and progesterone
cause heart attacks?

Coronary Heart Disease vs. Age



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

CAD and Female Hormones

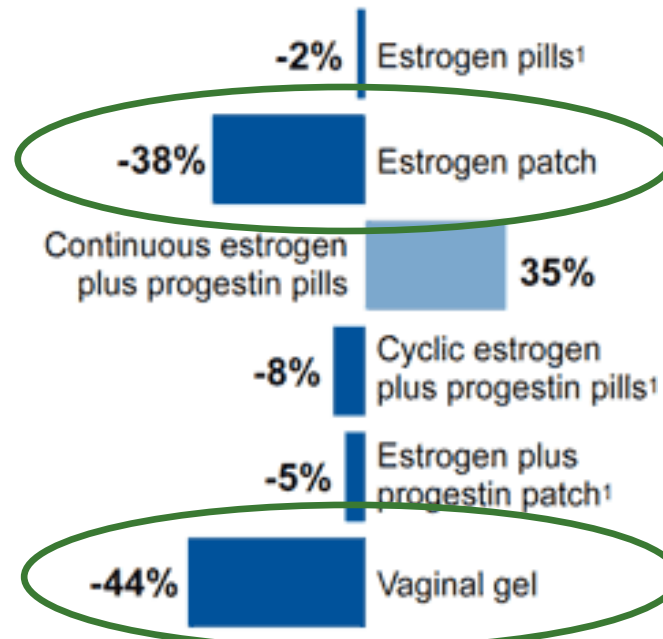
- ✦ After menopause, women's rate of CAD rises faster than men's! Higher risk than men after 65, and higher mortality after 70!
 - ✦ Early surgical menopause → ↑mortality, ↑atherosclerosis, 2-7x risk of heart attacks; earlier age=greater risk
- Colditz GA, Engl J Med 1987 Apr 30;316(18):1105-10
Rosenberg L, Am J Obstet Gynecol. 1981 Jan;139(1):47-51
- ✦ Bulk of Evidence: The youthful estradiol-progesterone-testosterone milieu is protective against CAD.

Estradiol vs. Cardiovascular Disease

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

Transdermal Estradiol Prevents Heart Attacks

Differences in heart attack risk in Danish hormone users compared with non-users:



1 – Not considered statistically significant.

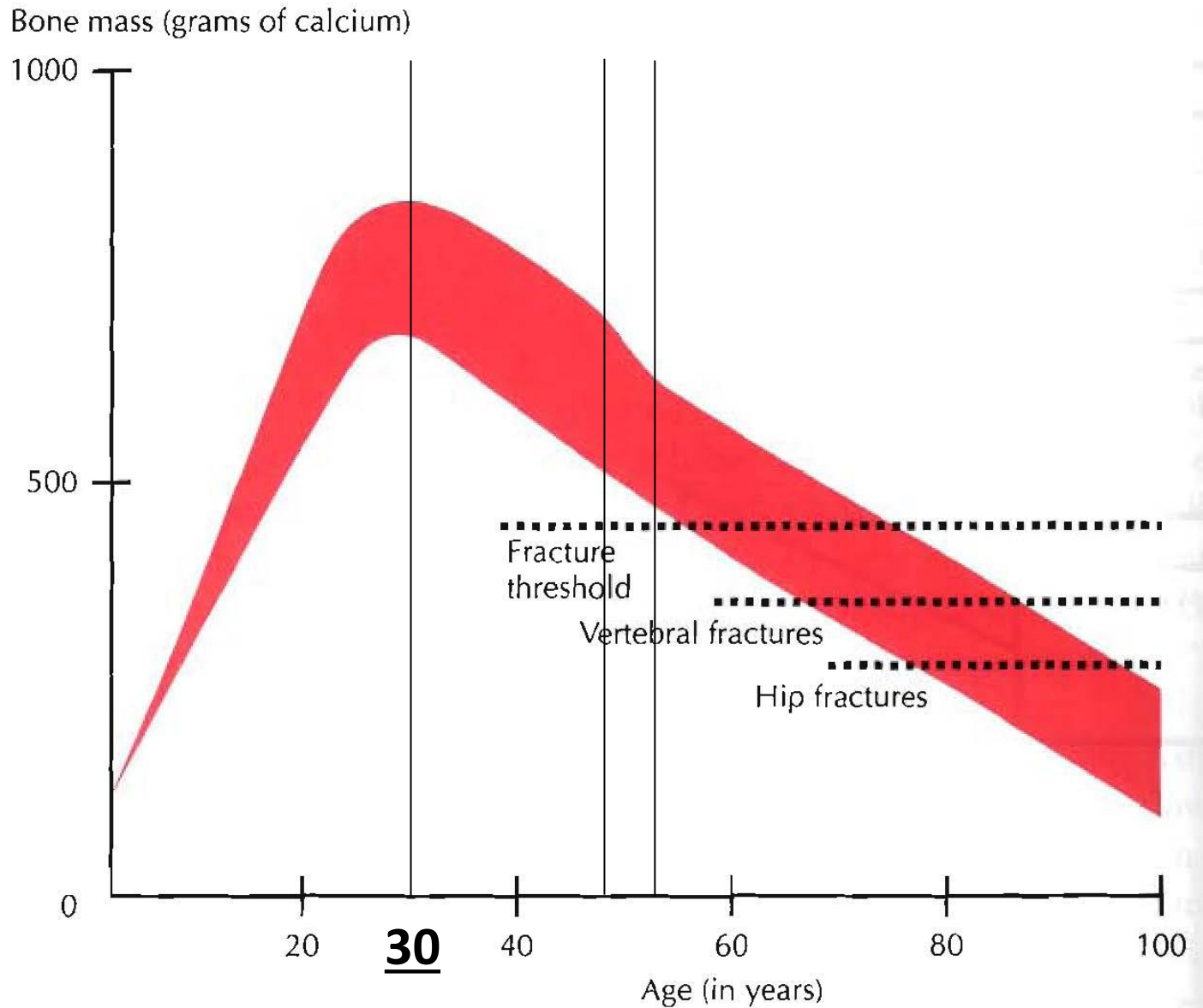
Source: European Heart Journal

By Frank Pompa, USA TODAY

Oral ERT Prevents Atherosclerosis

- ✦ Long-term Premarin[®] shown to reduce risk of **heart disease** in 40 observational and case-control studies
- ✦ 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 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
- ✦ Confounder: There's a problem with oral estrogens....

Changes in Women's Bone Mass with Age



Osteoporosis—Impact

- ✦ **Bone loss** occurs in menstruating women with lower estradiol and testosterone levels.

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

- ✦ **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% reduction** in cortical bone

- ✦ 50% of women >65 yrs. old have **spinal compression fractures**

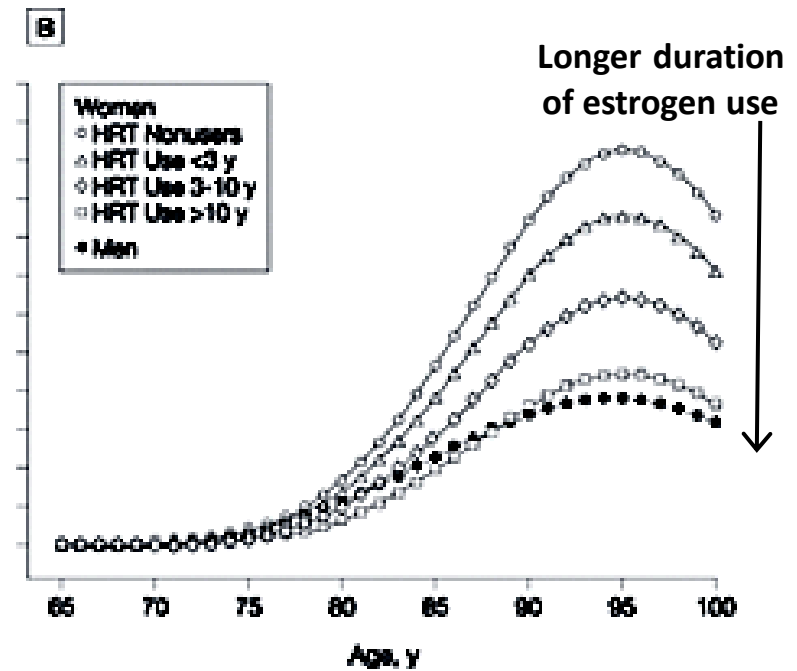
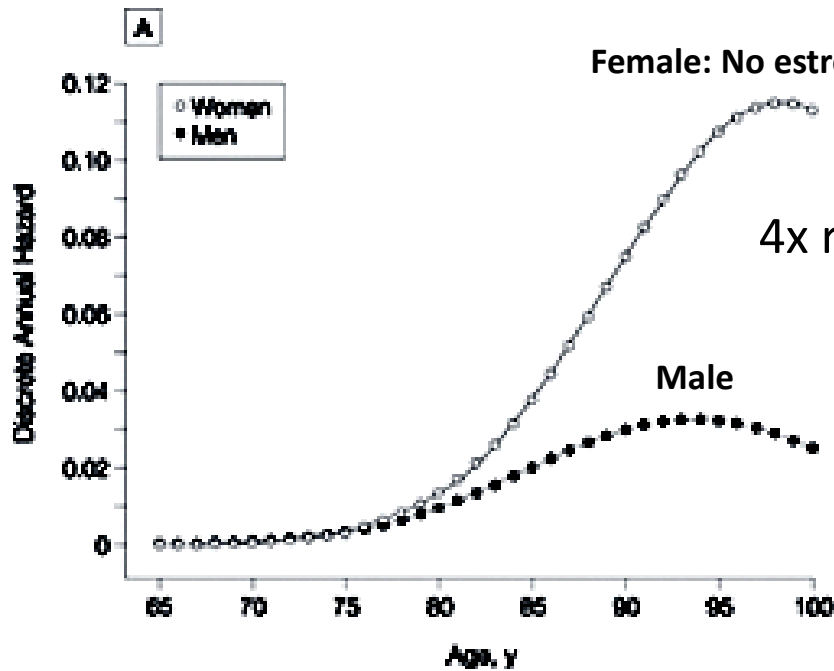
- ✦ 30% lifetime risk of **hip fracture** for 80 yr. old woman

Speroff L, Fritz M Clinical Gynecologic Endocrinology and Fertility, 7th Ed.

Osteoporosis

- ✦ A **hormone deficiency** disease—the proper prevention and treatment is **hormone restoration**.
- ✦ **Estradiol** prevents resorption of old bone while **testosterone** and **progesterone** 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
- ✦ **EPT therapy** increases both bone mineral density and collagen content, maintains **normal** bone remodeling
- ✦ Bisphosphonate drugs **poison** osteoclasts, **suppress** bone turnover → “rotting jaw”, poor diaphyseal fracture healing and non-traumatic femur/pelvic **fractures** after 8 years
- ✦ Vits. D3 (a hormone) and K₂ preserve bone mass
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

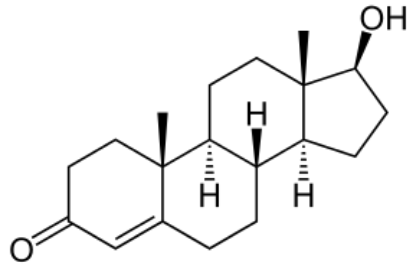
Bioidentical Hormone Restoration is the Best Medical Practice

- ✦ Youthful-Optimal hormone levels and balance improve health and quality of life
- ✦ **Logical:** If a hormone is **missing**, replace it! If **insufficient**, optimize it!
- ✦ Use **bioidentical molecules** = correct chemical structure; if not bioidentical, not a human hormone!
- ✦ Bioidentical HRT is the Best Medical Practice: insulin, levothyroxine, growth hormone, cortisol (hydrocortisone), etc.
- ✦ Also optimize **vitanutrients**: Multivitamin/Mineral, Vit.D: 40-60ng/ml, ferritin: 80-100pg/ml, magnesium, Vit C., Omega-3 fatty acids, etc.

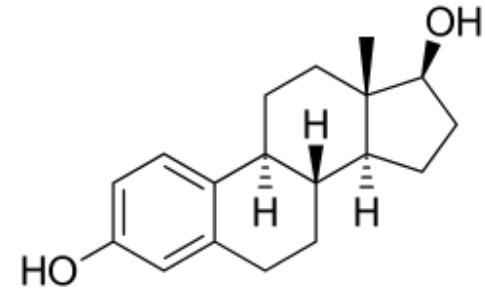
Q: Why does everyone think that HRT
for menopause is dangerous?

A: Pharmaceutical Hormone
Substitution

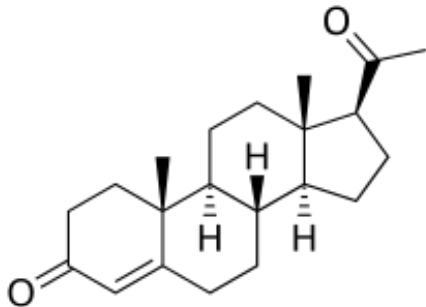
Human Steroid Hormones



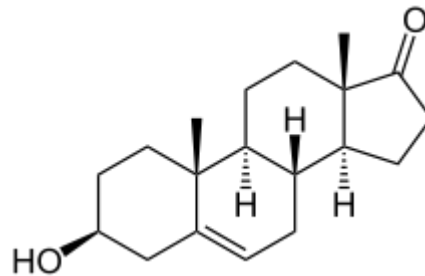
Testosterone



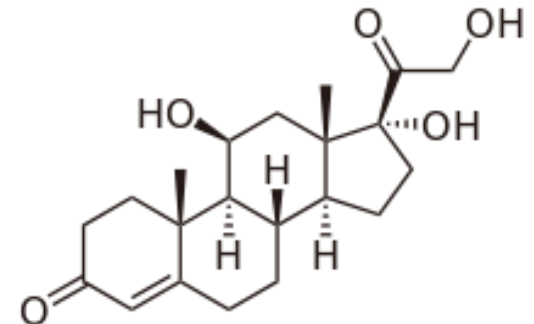
Estradiol



Progesterone



DHEA



Cortisol

Pharmaceutical “Hormone Replacement”

- ✦ Pregnant mare’s urine (Premarin®) approved in 1942
- ✦ Progesterone: first steroid synthesized from a plant molecule in 1940.
Poorly absorbed orally
- ✦ Orally-effective progestins were produced—norethindrone in 1952,
medroxyprogesterone acetate (Provera®) in 1956.
- ✦ For 70 years “HRT” has meant the use of non-human steroid molecules with hormone-like effects.
- ✦ Human hormones cannot be patented, limited profitability

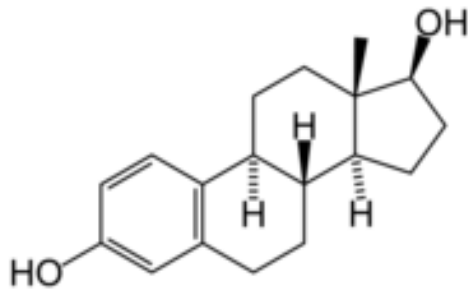
“HRT” has been “HST”

Hormone Substitution Therapy

- ✦ Progesterone substitutes: medroxyprogesterone acetate (MPA-Provera[®]) and 30+ other “**progestins**”
- ✦ Estradiol substitutes: CEE-Premarin[®], ethinyl estradiol
- ✦ Testosterone substitute: **methyltestosterone** in Estratest[®] (metabolizes to super-potent estrogen, ↑’d **breast cancer**)
- ✦ Widespread confusion due to careless nomenclature: “HRT”, “hormone”, “estrogen”, “progesterone” and “testosterone” often used for **hormone substitutes**.
- ✦ **Substitutes** are Drugs—not hormones; but all problems caused by **substitutes** are attributed to hormones as “drug class effects”.

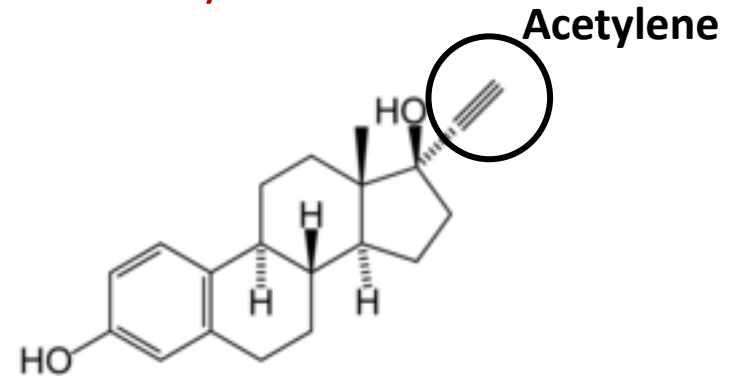
Oral Contraceptives

Estradiol



Hormone

Ethinyl Estradiol



Drug

EE is much more **thrombogenic** than oral **estradiol**.

EE cannot be inactivated by normal oxidation.

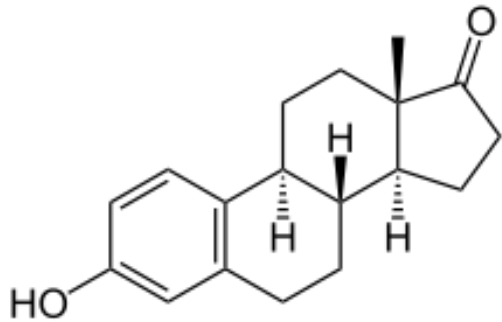
EE does not interact with estrogen receptor β .

EE is 12,000-60,000 times more potent by weight.

Premarin[®]

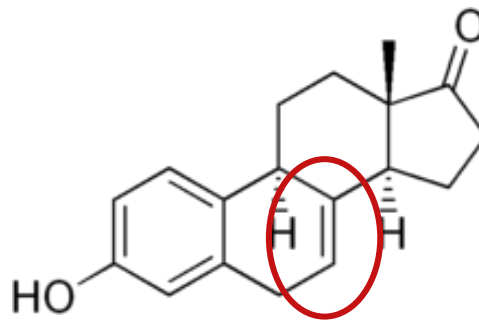
Conjugated Equine Estrogens

Human



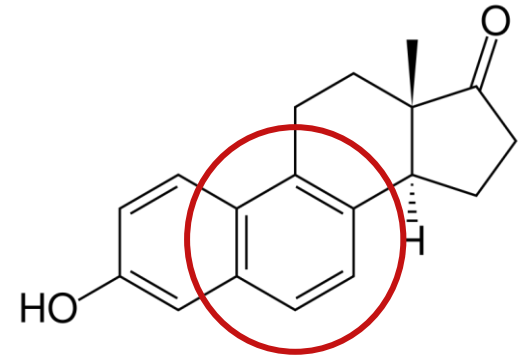
Estrone

Horse



Equilin

Horse



Equilenin

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

2002 WHI Study—Premarin[®] Arm

- ✦ **Adverse CV effects** in the first year (strokes, blood clots)
- ✦ Long-term reduction in CHD (anti-atherosclerotic effect).
- ✦ Reduced CHD and **mortality** when started in 50-59yr. olds, but increased when started in 70-79yr olds (with atherosclerosis).
- ✦ Hip fractures **reduced** by 39%

Oral Estrogens Promote Thrombosis

- ✦ First-pass effect on the liver → ↑clotting factors → blood clots, strokes, heart attacks especially in the first year, especially in persons with coagulation disorders.
 - ✦ Transdermal estradiol does not promote thrombosis!
- “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 delivery mimics natural secretion.

CV Risk Factors: Oral ≠ Transdermal E

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 *estradiol*

| <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 |

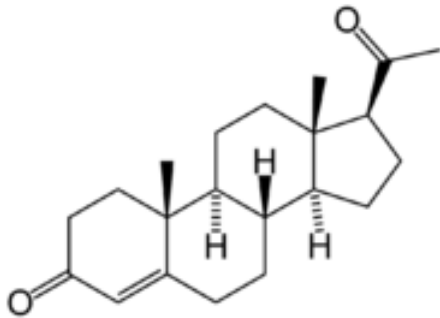
APC, activated protein C; HDL, high density lipoprotein; LDL, low density lipoprotein; Apo, apolipoprotein; NO, nitric oxide; IL, interleukin; TNF, tumor necrosis factor; PAI-1, plasminogen activator inhibitor-1; IGF, insulin-like growth factor; IGFBP; insulin-like growth factor-binding protein; GH,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

WHI Study—Prempro[®] Arm

- ✦ Adding Provera[®] to Premarin[®] caused additional heart attacks, strokes, breast cancer, and dementia (prob. vascular).
- ✦ **Thousands** of lawsuits pending—drug companies running legal-protection propaganda campaign
- ✦ Women are told, “All HRT is dangerous!”
- ✦ **Negative** results of WHI have never been documented with transdermal estradiol with progesterone

Progesterone vs. Provera[®]

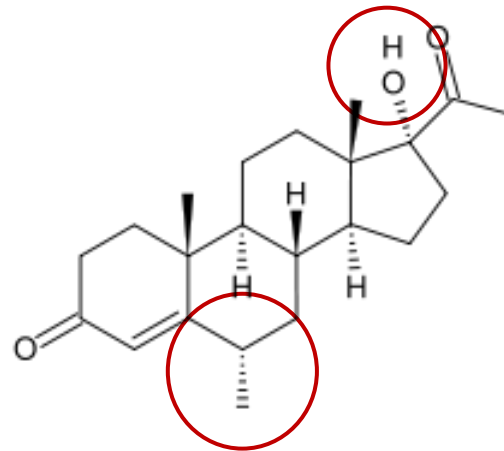
Progesterone



Hormone

Medroxyprogesterone acetate

≠



Drug

Prempro[®] increases cellular **proliferation** and breast **density** and affects 2500 genes; estradiol plus progesterone does not increase proliferation or density and affects only 600 genes.

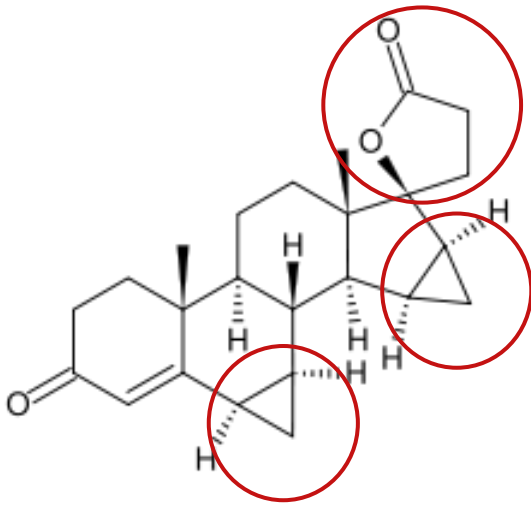
Scientific studies show that:

Provera[®] ≠ Progesterone

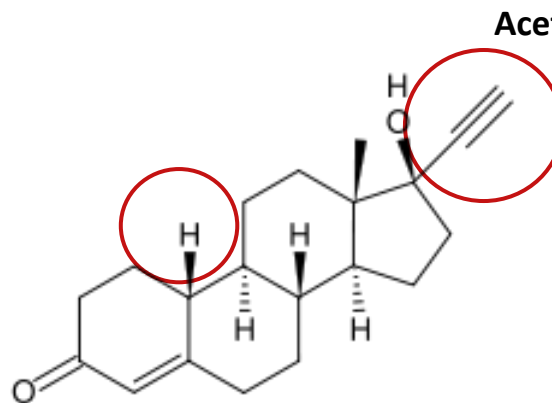
- Birth defects
 - Depression
 - Insomnia, irritability
 - Reduces neuroprotection
 - Fluid retention
 - Glucocorticoid-like effects
 - Raises blood sugar
 - Vasoconstriction
 - Smooth muscle proliferation
 - Increases blood clotting
 - Worsens lipid profile
 - Causes heart attacks
 - Increases MMP activity
 - Increases estrogenic stimulation of breasts
 - Promotes breast cancer
- Hormone of Pregnancy
 - Improves mood
 - Improves sleep
 - Neuroprotective
 - Diuretic
 - Anti-glucocorticoid
 - 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

Progestins \neq Progesterone

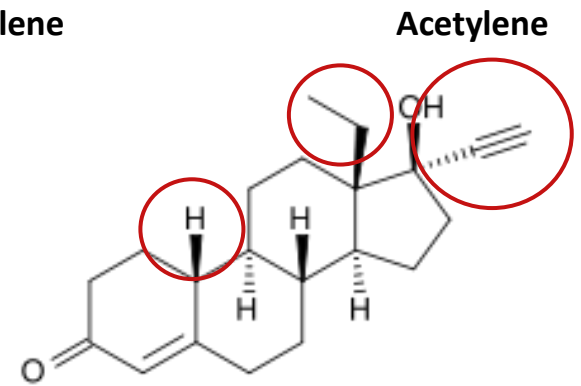
Drospirenone (Yasmin®)



Norethisterone



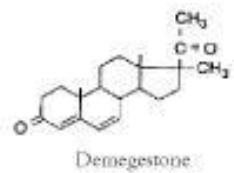
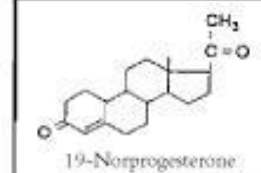
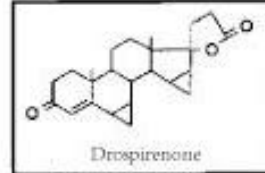
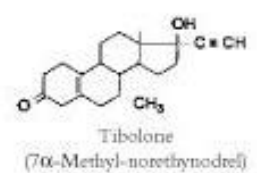
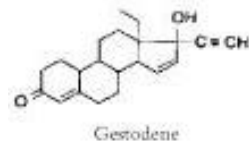
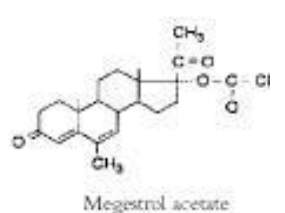
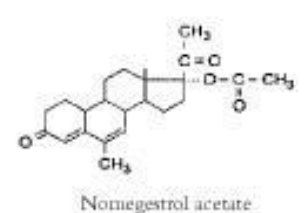
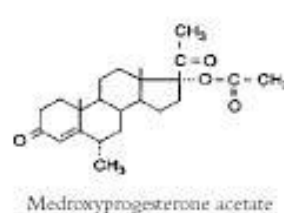
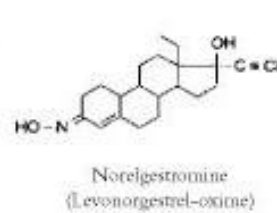
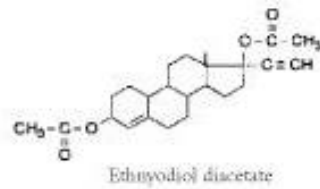
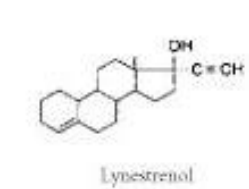
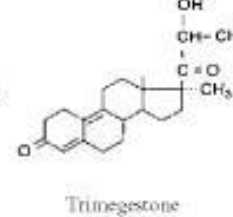
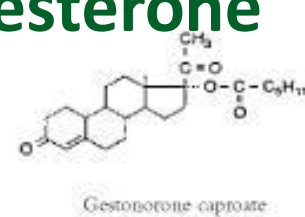
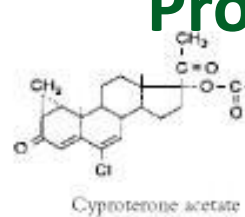
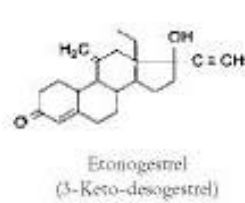
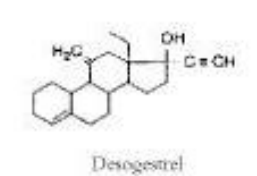
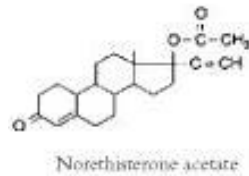
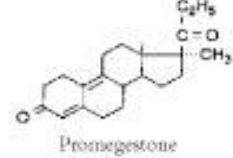
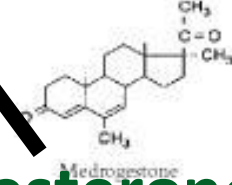
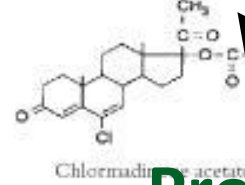
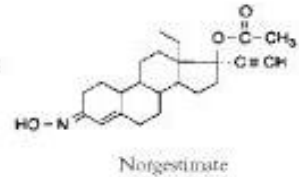
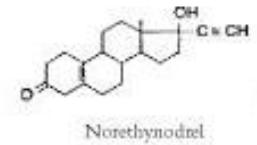
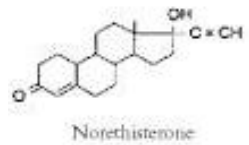
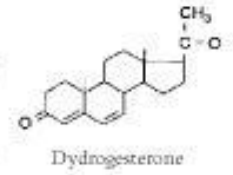
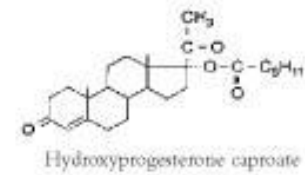
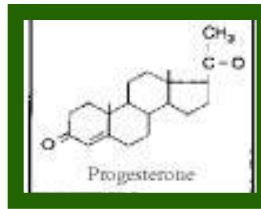
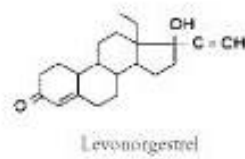
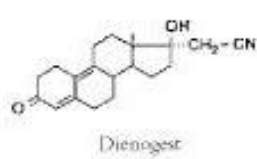
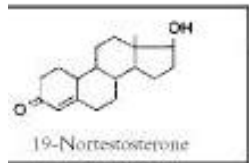
Levonorgestrel



Most **progestins** increase **breast cancer** risk (RR~1.4 to 2.0)

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

Progestin Zoo



Progesterone

Kuhl, Climacteric 2005;8(Suppl 1)

Each progestin has a different spectrum of androgenic, estrogenic, glucocorticoid, and progestational effects.

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 (progestins) 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

Any Questions about EPT benefits and
safety or dangers of pharmaceutical
HST?

Next: How to do bioidentical EPT
restoration

Principles of Bioidentical EPT Therapy

- ✦ Clinical Endocrinology: Adjust doses by symptoms first, serum levels second.
- ✦ Eliminate symptoms/signs of **deficiency** while producing no symptoms/signs of **excess**
- ✦ No side effects: all problems that occur are due to dosing, balance, route or other hormonal or medical issues.
- ✦ For peace of mind: Have patient sign a consent form.
- ✦ Provide written instructions for using hormones, preventing transfer, adjusting doses (see handouts).

Serum Testing for Menopause

- ✦ Good to get baseline levels even in menopause—show patient.
- ✦ Pre-treatment: order total and free estradiol, total and free testosterone; progesterone always low.
- ✦ Free hormone level best represents bioavailable hormone
- ✦ Cannot use saliva testing to monitor **EPT** therapy—overreacts to transdermal steroid hormones → spuriously high results
- ✦ To monitor replacement: have blood drawn ~12 hrs after daily dose for best estimate of 24hr average. Typically: AM test after bedtime application of hormones.

FDA-Approved Bioidenticals

- ✦ Estradiol patch (Climara[®], Vivelle[®], etc.)
- ✦ Estradiol gel (Estrogel[®], Divigel[®], etc.)
- ✦ Estradiol vaginal ring (Femring[®])
- ✦ Progesterone capsules (Prometrium[®], generic)
- ✦ Progesterone vaginal gel (Crinone[®])
- ✦ No FDA-approved testosterone product for women

Problems: weak, inconvenient, fixed doses, and/or expensive

Problems with FDA-Approved E&P

- ✦ **Estradiol** patches: Adhesion/allergy problems, otherwise very good. Estradiol level should be checked mid-way between patch changes.
- ✦ **Estradiol** gels: very expensive (\$200/mo)
- ✦ Oral **progesterone-in-oil** capsules are inefficient: immunoassay progesterone levels are 80% metabolites, quite sedating.
- ✦ 200mg oral Prometrium[®] yields same 24hr whole blood LC/MS/MS progesterone levels as 80mg **progesterone** in transdermal cream.
Hermann AC et al., J Clin Pharmacol 2005;45:614-619
- ✦ Oral **progesterone** caps best take vaginally (100mgs) or punctured to apply oil to skin (200mgs).

Compounded Bioidentical Hormones

- ✦ Locally made from USP-certified micronized hormone powders
- ✦ Standardized compounding practices with PCCA (Professional Compounding Centers of America) and other organizations.
- ✦ Completely customizable delivery systems and concentrations
- ✦ Can make **testosterone** cream, **progesterone** cream, **EPT** combo creams, sublingual **progesterone** (No FDA-approved equivalents)
- ✦ Inexpensive—Often less than co-pays for FDA-approved bios.
- ✦ Physician-monitored: adjust dose by clinical effects and serum levels



09.13.2014

Estradiol Restoration

- ✦ 3mg/0.5ml cream, 0.1ml (1 line) applied to face or neck at bedtime, ↑ as needed to 0.3ml. Adjust strength of cream if needed.
- ✦ Good for facial skin tone: **E2** increases skin collagen.
- ✦ Clinical Dosing: eliminate hot flashes, vaginal dryness, insomnia; avoid breast fullness-tenderness, vaginal bleeding, fluid retention
- ✦ 12 hr. serum **estradiol** is usually 30-125pg/ml (similar to follicular phase). **Free estradiol** usually 0.5 to 1.5pg/ml (More accurate measure—same as **male** free estradiol range).
- ✦ No need for estriol (E3), a weak metabolite of **E2**.
- ✦ Avoid transfer to other persons or pets (See handout)

Progesterone Restoration

- ✦ 100mg sublingual tablet at bedtime, better absorbed than cream
- ✦ Pulse therapy: levels very high at 3-6 hrs., low-luteal at 12 hrs.
- ✦ 100 mg in cream, serum levels (2-4 ng/dL) underestimate effect.
- ✦ Sufficient **progesterone** prevents breast tenderness, bleeding
- ✦ For unusual bleeding tendency use vaginal tabs/cream/caps.
- ✦ **Progesterone** is SAFE at any dose. Too much → sedation, heartburn, constipation
- ✦ For premenopausal menorrhagia or early breakthrough bleeding try twice-daily sublingual P or vaginal P in luteal phase or continuously

Testosterone Restoration

- ✦ 2mg/0.2ml Versabase cream, apply 0.1ml (1 line) to inner labia or 0.2ml to back of knees.
- ✦ Best absorbed genitally, improves libido and vaginal moisture, no clitoromegaly reported.
- ✦ If not tolerated labially, use higher strength/amount to inner thighs or back of knees (no local hair growth)
- ✦ Lower T dose for excess acne or facial hair—but a few pimples, more body hair are natural effects of youthful **testosterone** levels!
- ✦ Good dose: 12 hr. serum total **testosterone** usually high, but bioavailable **testosterone** above mid-range (range 1 to 8.5pg/ml).
- ✦ More androgen effect than **testosterone** levels suggest because DHT is higher with transdermal, especially genital application.

Troubleshooting

- ✦ Recurrent bleeding/spotting may occur due to submucosal fibroid, polyp, or adenomyosis; try lower estradiol dose, higher progesterone dose or vaginal progesterone.
- ✦ Postmenopausal cancer-surveillance guidelines do not apply: Endometrial evaluation only if bleeding persists in spite of dose changes and off EP therapy.
- ✦ If hot flashes worsen with estradiol, lower dose then increase very slowly, try AM dosing
- ✦ Inability to tolerate estradiol or progesterone may be due to hypocortisolism (a.k.a. adrenal insufficiency).
- ✦ Hair loss: ↑ estradiol, ↓ testosterone (some women have androgen-sensitive alopecia)

Women with Breast Cancer?

- ✦ Almost all studies of **estrogen/progestin** (pro-proliferative) therapy in women with breast cancer show no increase in recurrence rates.
- ✦ One human and two rat studies indicate that **bioidentical estradiol-progesterone** therapy is an effective preventative and treatment for **breast cancer**.
- ✦ **Estradiol-deprivation** therapies (tamoxifen, aromatase inhibitors) only reduce 5-to-10 year recurrence rates, they do not cure cancer; and have a high cost in quality of life and health.
Plotkin, D. <http://www.theatlantic.com/past/issues/96jun/cancer/cancer.htm>
- ✦ **Estradiol-progesterone-testosterone** replacement is not contraindicated and may reduce recurrence rates due to the **anti-proliferative** effects of **progesterone**.
- ✦ **EPT therapy** can be combined with aromatase inhibitor—as the latter will reduce intra-mammary estradiol production while EPT maintains systemic health.

For More Information

- ✦ See presentation, handouts, practice forms on CD
- ✦ www.hormonerestoration.com
- ✦ Essays on [Hormone Restoration](#)
- ✦ Thousands of abstracts under [The Evidence](#)
- ✦ Contact me: henry@hormonerestoration.com

Q: Why don't physicians and the public know about the benefits and safety of bioidentical HRT?

A: Pharmaceutical Corporation Clout

HRT Information Warfare

- ✦ After WHI report, lawsuits piled up and women switched from Prempro® to pharmacy-compounded **bioidentical hormones**.
- ✦ US professional associations proclaimed “All HRT is alike”; FDA-approved and compounded **bioidentical hormones** had the same risks as all other FDA-approved “hormone products”.
- ✦ The North American Menopause Society (NAMS) published an anti-bioidentical article —confounding bioidentical HRT with questions surrounding compounding and saliva testing.

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

- ✦ “Bioidentical” ridiculed as a “marketing term”, “fad”, “snake oil”.
- ✦ Muddying the waters: NAMS advised that **progesterone** and **progestins** now be called “**progestogens**”!
- ✦ NAMS tells women and their doctors: “Use any FDA-approved **progestogen**, but don’t use compounded **progesterone**”.

ACOG Helps Big Pharma

October 31, 2005, ACOG NEWS RELEASE “There is no scientific evidence to support claims of increased efficacy or safety for individualized estrogen or progesterone regimens prepared by compounding pharmacies,ACOG recommends that they 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.” ...Furthermore, hormone therapy does not belong to a class of drugs with an indication for individualized dosing (!?!)

ALL LIES!

ACOG, NAMS and The Endocrine Society are funded by **Pharmaceutical Corporations.**

Conflict of Interest: professional associations and policy makers should have zero (0) industry funding.

Rothman DJ et al, Professional medical associations and their relationships with industry:
a proposal for controlling conflict of interest. JAMA. 2009 Apr 1;301(13):1367-72.

Wyeth Jumps In

- ✦ October 2005: Wyeth (maker of **Prempro**[®]) files “citizen petition” asking FDA to impose restrictions on physicians’ ability to prescribe and pharmacists’ ability to make compounded **bioidentical hormones**!
- ✦ Demands that compounding pharmacies cease promoting **bioidentical hormones** as more natural (??) or safer (??) than its **dangerous hormone substitutes**!
- ✦ Demands the same warnings for compounded **bioidentical** hormone preparations as for its **dangerous hormone substitutes**
- ✦ Motives: Legal protection (**Prempro**[®] lawsuits) and market share (**Prempro**[®] is still being prescribed!)

HRT Wars: Conclusions

- ✦ Women have been victimized by propaganda from pharmaceutical corporations and the “professional” associations that they fund.
- ✦ Things are changing: Recent guidelines from International Menopause Society, NAMS and The Endocrine Society contain statements about the greater safety of **transdermal estradiol** and **progesterone**. (“may not have the same risks...”)
- ✦ **Estradiol (transdermal)**, **progesterone** and **testosterone** restoration will soon be standard medical practice.