I) Arguments against the use of non-bio-identical estrogens and non-bio-identical progestogens in women:

1) The two major studies that have brought the present controversy on the use of female hormone replacement have shown that non-bio-identical hormones may risk of disease

Women’s Health Initiative (WHI) study: non-bio-identical hormones increase the cardiovascular and breast cancer risks


Facts:
Premature stop of this large double-blind placebo-controlled study because of the increased risk of (RR) invasive breast cancer (1.26) and increased global risk index (1.15); The global risk would have remained negative at the end of the study, even if the results for prevention of cardiovascular disease would have inversed (low probability))

Critics:
• The population of the study is not a representative population
  • Older patients (mean age: 63 years); patients have not been under H.R.T. before inclusion (period of no HRT between menopause and 63 yrs) => no real « primary prevention »:
  • Not a healthy population: 2/3 of patients were overweight (BMI≥25Kg/m2), 1/3 had morbid obesity (BMI≥30Kg/m2); 35.7 % were hypertensive or treated for hypertension; 12.5 % were hypercholesterolemic; 4.4 % were diabetic or treated for diabetes
  • Toxic factor: about 50 % of the 8,500 women on HRT were smokers or had been smokers (Mueck AO, Seeger H. Smoking, estradiol metabolism and hormone replacement therapy. Arzneimittelforschung. 2003;53(1):1-11. Women’s University Hospital, Tubingen, Germany. endo.meno@med.uni-tuebingen.de)
  • Not a representative population of European patients
  • The medication is not a representative and safe female hormone replacement therapy (association of conjugated estrogens with medroxyprogesterone acetate)
    • It is a popular medication in the USA, not in Europe
    • The type of hormones is not bio-identical
    • The route of administration for estrogens is the oral one. Results are possibly/probably not true for transdermal estrogens and for estradiol and progestogens of bio-identical structure (Stevenson JC, Whitehead MI. Hormone replacement therapy. BMJ. 2002 Jul 20;325(7356):113-4)
  • Not an easy study (JAMA editorial)
    • high drop-out rate: 42% of women have stopped the treatment during the study
    • 10.7% of placebo group have began a H.R.T.

Million Women Study: > 99.97% of the hormones used where non-bio-identical hormones, which increased the breast cancer risk

(Critics: Same critics as above; Additional:

- the study was not a double-blind placebo-controlled study, but an observational study based on patient’s reports.
- many of the participants had switched from one medication over to another during the study.
- from the information that we have received, only about 300 of the one million women of the study had taken transdermal estradiol therapy, almost all on the estradiol patch, which may provide less constant estrogen levels (and of those only some 30 had taken the estradiol gel – that came out in the U.K. as official brand only two years after the start of the study and two years before its end)
- none of the women had taken progesterone, (micronized, the bio-identical one), solely synthetic derivatives of progesterone were taken

2) Other studies that show that estrogens with a NON BIO-IDENTICAL (foreign-to-the-human-body) structure, may adversely affect the body:

2-a) Absorption of non-bio-identical estrogens provides abnormal estrogens in the blood:

Treatments with equine estrogens (the Prempro of the WHI and Million Women studies) supply the blood with abnormal estrogens. Equine estrogens contain estrone sulfate (53-61%), equilin sulfate (23-30%) equilenin, 17 a-dihydroequilin, 17 alpha-estradiol, 17 a-dihydroequilenin and numerous other horse estrogens


Treatments with ethinylestradiol (the Million women study):


2b) non-bio-identical hormones are almost always provided through the ORAL ROUTE, which is not the best route, nor a totally safe one:

2b-1) Treatments with oral estrogens provide imbalanced serum levels of estrogens and urinary levels of estrogen metabolites (an abnormally high serum estrone level and an abnormal increase of urinary 16-alpha-hydroxy-estrone)


2b-2) Treatments with oral estrogens excessively increase the serum levels of the plasma binding proteins
How? Oral estrogens, after absorption in the intestinal tract, are transported to the liver where they accumulate. The liver produces under this “estrogen dominance” excessive amounts of hormone plasma binding proteins, resulting in high serum levels of the plasma binding proteins, which bind greater amount of various hormones in the serum, thus reducing the amount of hormones bioavailable for the target cells.

2-b-3) Treatments with oral estrogens reduce the levels and activities of other hormones

Treatments with oral estrogens reduce serum IGF-1 levels and thus GH metabolic activity


Treatments with oral estrogens reduce the excretion of melatonin metabolites and thus melatonin activity


Treatments with oral estrogens reduce serum free thyroid hormones, in particular serum free T3, and thus thyroid activity


Treatments with oral estrogens reduce cortisol levels, and thus glucocorticoid activities


Treatment with oral estrogens reduce free and total testosterone, DHT, DHEA, free cortisol, and thus androgen and glucocorticoid activities


2-c) Non-bio-identical hormones such as those of oral birth-control pills may not be better through the transdermal route (as transdermal patches): They cause similar and on some points worse adverse effects than through the oral route.
They increase similarly or even to a greater extent the levels of the plasma binding proteins
They may cause similar or even to a greater extent reductions of hormone activities


2c-1) **The transdermal contraceptive patch** (Ortho Evra/Evra, 1 patch per week of 20 µg ethinyl estradiol with 150 µg norelgestromin, the active metabolite of the progestogen norgestimate, structurally related to 19-nortestosterone)

- The transdermal contraceptive patch provides higher levels of ethinylestradiol and SHBG, than the oral pill, but similar increase of on CBG


The transdermal contraceptive patch provides a higher level of SHBG and similar lowering effect on key serum androgen levels (DHEAs, free testosterone and androstanediol glucuronide) as oral contraceptive pills


The transdermal contraceptive patch provides higher levels of SHBG and TBG and greater increase of CRP compared to the oral pill


The transdermal contraceptive patch causes a higher incidence of breast pain, dysmenorrhoea and application site reactions than the oral pill


The transdermal contraceptive patch causes a similar increase in risk of nonfatal venous thromboembolism for the contraceptive patch as for the oral contraceptive pills


The transdermal contraceptive patch causes similar unfavourable lipid changes: increases in total cholesterol and total triglycerides compared to the oral group

2c-2) **Other transdermal contraceptive patch**: ethinylestradiol/gestodene (.9 mg ethinylestradiol and 1.9 mg gestodene)

2c-3) **The vaginal contraceptive ring** (Nuvaring, 1 per 3 weeks; 2.7 mg of ethinylestradiol and 11.7 mg of etonogestrel, which supply 12 µg of etonogestrel and 15 µg of ethinylestradiol per day) supplies much less ethynylestradiol to the body


2d) **Studies where oral and/or structurally non-bio identical estrogen treatments were associated with adverse effects on the cardiovascular system**

Treatments with oral estrogens, including conjugated estrogens, disturb blood coagulation:
Treatments with oral estrogens increases factor VII activity


Treatments with oral estrogens reduce tissue factor pathway inhibitor, a major inhibitor of the extrinsic coagulation pathway, and increase C-reactive protein, a component of the acute phase


Treatments with high doses of oral estrogens significantly increase serum alpha 1-antitrypsin and plasminogen levels


Treatments with oral estrogens significantly reduce antithrombin III and protein S activities


Treatments with oral estrogens increase in matrix metalloproteinase-9 within the vessel wall: could digest and weaken fibrous caps of vulnerable plaques, thus provoking thrombosis


Treatments with oral estrogens increase the risk of venous thromboembolism, especially during the first year


Treatments with oral estrogens increase the risk of ischaemic stroke among postmenopausal women


Treatments with oral estrogens and tibolone significantly increase serum CRP, while transdermal estradiol has no significant effect on serum CRP


2e) Studies where treatments with structurally NON BIO-IDENTICAL estrogens were associated with an increased breast cancer risk

In vitro treatments with conjugated estrogens excessively stimulate epithelial proliferation in breast tissue, an effect worsened with the addition of medroxyprogesterone acetate (MPA)
45. Hofseth LJ, Raafat AM, Osuch JR, Pathak DR, Slomski CA, Haslam SZ. Hormone replacement therapy with estrogen or estrogen plus medroxyprogesterone acetate is associated with increased epithelial proliferation in the normal postmenopausal breast. J Clin Endocrinol Metab. 1999 Dec;84(12):4559-65.

**Treatments with conjugated or other non-bio-identical estrogens increase the breast cancer risk**


**Studies with associations between hormone replacement treatments and increased risk of breast cancer**

Studies where female hormone replacement treatments (generally with oral, non-bio-identical estrogens and synthetic progestogens) were associated with an increase in risk of breast cancer


**Studies that contest the validity of the above-mentioned studies**


Studies where female hormone replacement treatments (generally with oral, non-bio-identical estrogens) were associated with an increase in risk of breast cancer in women with familial breast cancer

56. Steinberg KK, Thacker SB, Smith SJ, Stroup DF, Zack MM, Flanders WD, Berkelman RL. A meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer. JAMA 1991 Apr 17;265(15):1985-90 (higher risk of breast cancer in women with familial history of breast cancer if ever use of estrogen therapy; critic: other studies have shown that estrogen replacement did not induce a greater risk of breast cancer, but did reduce the overall mortality of women with familial history of breast cancer, see further)

**3) Studies that show that progestogens with NON BIO-IDENTICAL structure may adversely affect the body:**

3a) **Studies where treatments with synthetic derivatives of progesterone (medroxyprogesterone acetate (MPA) and other progestogens) were associated with adverse effects on the cardiovascular system**

Treatments with structurally modified progestogens block the beneficial effects of estrogens on the cardiovascular system (not the case with natural progesterone)


62. Williams JK, Hall J, Anthony MS, Register TC, Reis SE, Clarkson TB. A comparison of tibolone and hormone replacement therapy on coronary artery and myocardial function in ovariectomized atherosclerotic monkeys. Menopause 2002 Jan-Feb;9(1):41-51


Treatments with MPA have adverse effects on cardiovascular parameters, increasing the serum triglycerides


Treatments with MPA have adverse effect on coronary arteries, increasing arteriosclerosis (not the case with bio-identical progesterone)


Treatments with MPA stimulate atheroma development (no effect of norethisterone)


Treatments with structurally modified progestogens may stimulate vasospasm of the coronary arteries (not the case with natural progesterone)


Progestins increase the risk of venous thrombo-embolic events, but increase is small compared to the other benefits


3b) Studies where treatments with progestogens that have a NON-BIO-IDENTICAL STRUCTURE may increase the possibility of breast cancer development

Some progestins (pregnanes) derived from progesterone stimulate apoptosis leading to breast cancer cell death; most cannot stimulate breast cancer cell multiplication; others such as estranes or gonanes derived from testosterone, stimulate breast cell multiplication in vitro through an estrogen receptor-mediated pathway


II. Arguments for the use of bio-identical estrogens and bio-identical progesterone in women

1) Studies that show that transdermal and bio-identical estradiol may be superior to oral and/or non-bio-identical estrogens. Transdermal estradiol may avoid the adverse effects generally attributed to oral and/or non-bio-identical estrogens.

1a) Transdermal or implant estradiol treatments provide normal estrone-estradiol levels, while oral estrogen treatments do not


82. Lippert TH, Seeger H, Mueck AO. Estradiol metabolism during oral and transdermal estradiol replacement therapy in postmenopausal women. Horm Metab Res. 1998 Sep;30(9):598-600


1b) Transdermal estradiol treatments have no adverse effects on hemostatic factors and other cardiovascular risk factors (no CRP increase e.g.), while oral estrogen treatments do


1c) Transdermal estradiol treatments have a higher beneficial effect on weight, and lean and fat mass than oral estrogen treatments


Garvan Institute of Medical Research, St. Vincent's Hospital, Sydney NSW 2010, Australia

1d) Transdermal estradiol treatments spare the liver (no liver accumulation of estrogens), while oral estrogens do not (first passage through the liver after absorption, resulting in an excessive accumulation of estrogens in the liver).

1e) Transdermal estradiol treatments do not excessively increase the levels and liver production of plasma binding proteins such as SHBG, TBG, transcortine, GHBP, etc, while oral estrogens do.


1f) Other beneficial influences of transdermal estradiol compared to oral estrogens


1g) Study where treatments with parenteral (especially transdermal) BIO-IDENTICAL estradiol proved to be safer than oral estradiol

Study where treatments with intravenous estradiol stimulate less tumour development than oral estradiol in animals


1h) Studies where bio-identical and parenteral, in particular transdermal, estrogen treatments were associated with beneficial cardiovascular effects: more efficient and safer

Studies where low bio-identical estradiol levels are found in premenopausal women with coronary heart disease


2) Studies with beneficial cardiovascular effects of estrogen therapy, generally obtained with the use of transdermal and bio-identical estradiol

Treatments with transdermal estradiol cause vasodilatation of the brachial and forearm arteries in postmenopausal women


Treatments with oral estradiol causes vasodilatation of the brachial artery in postmenopausal women


Treatments with intracoronary or intravenous estradiol cause vasodilatation and increased distensibility of coronary arteries


Treatments with subcutaneous implants of 17-beta estradiol reduce coronary artery disease in female monkeys


Treatments with subcutaneous injections of 17-beta-estradiol protect dogs against myocardial ischemia


Treatments with intravenous 17-beta-estradiol protect cats against acute myocardiac ischemia


Treatments with transdermal estrogen reduce angina in postmenopausal women with angina and normal coronary arteries


Treatments with implants of estradiol protect arteries of rats against atherosclerosis: prevent LDL-binding to arterial wall, reduce endothelial layer permeability


Overview on vascular protective effects of estrogen


Treatments with oral estradiol cause vasodilatation and increased distensibility of arteries

Treatments with transdermal estradiol reduce the carotid artery wall thickness and thus atherosclerosis in postmenopausal women


3) Studies where structurally BIO-IDENTICAL, especially TRANSDERMAL, estradiol treatment was shown to be breast cancer safer than treatments with non-bio-identical estrogens

EXOGENOUS BIO-IDENTICAL ESTRADIOL

In vitro study where a treatment with estradiol provided less epithelial proliferation than with conjugated estrogens in breast tissue, addition of bio-identical progesterone was even more reassuring as it greatly reduced the moderate bio-identical estradiol-induced proliferation


A study where the treatments associating transdermal estradiol to a progestogen other than MPA do not significantly increase the breast cancer risk (83% of participants took transdermal estradiol and other progestins than MPA were used)


ENDOGENOUS BIO-IDENTICAL ESTRADIOL: Studies where high levels of endogenous estrogens are associated with less breast cancer or longer survival after breast cancer

Studies where high levels of endogenous BIO-IDENTICAL estrogens are associated with a lower incidence of cancer or longer survival after breast cancer


A study where a high level of bio-identical estradiol at the moment of tumour surgery is associated with a better prognosis


Studies where increased levels of bio-identical estrogens (such as those found in mature young women compared to the levels of girls before puberty) are associated with a lower cancer mortality


Studies where a high level of estriol compared to estrone and estradiol may be associated with a reduced incidence of breast cancer


Studies where breast cancer tumours rich in estrogen receptors (that thus responds well to estrogens) had a better prognosis (more differentiated, less malignant tumour)


TRANSDERMAL BIO-IDENTICAL ESTRADIOL: Studies where treatments with estrogens taken by TRANSDERMAL ROUTE were associated with an increased risk of breast cancer or of conditions that may predispose to breast cancer

A high urinary excretion of 16-alpha- OH-estrone is associated with increased risks of mammary hyperplasia and breast cancer


Treatments with oral estradiol cause a major increase in urinary 16-alpha- OH-estrone, not the case with transdermal estradiol


Treatments with oral estrogens induce supraphysiological increases in estrone sulphate and estrone serum levels, not the case with transdermal estradiol

4) **Studies with beneficial or neutral effects of BIO-IDENTICAL PROGESTERONE on the cardiovascular system:**

**Treatment with vaginal progesterone gel delays exercise-induced myocardial ischemia in postmenopausal women with coronary heart disease and/or previous myocardial infarction**


**Treatments with transdermal or intravenous progesterone (4 weeks) protect against severe prolonged coronary vasoconstriction, and reduce lipoprotein (a) in non and preatherosclerotic and atherosclerotic female monkeys**


**Treatments with intravenous progesterone increase coronary blood flow in pigs**


**Treatments with progesterone in vitro relax isolated animal coronary smooth muscles cells and arteries**


**Treatments with progesterone have no negative effect on estradiol-induced protection of coronary arteries**


5) **Studies with protective or neutral effects of bio-identical progesterone against breast cancer**

5-1) **EXOGENOUS BIO-IDENTICAL PROGESTERONE:**

**Studies where progesterone/progestogen treatment reduced the breast cancer risk in women with breast cysts**


Treatments with transdermal estradiol alone or combined to a synthetically modified progestin increases the BC risk, but combined to bio-identical progesterone causes a -10% decrease of the breast cancer risk


5-2) ENDOGENOUS BIO-IDENTICAL PROGESTERONE:

Studies where lower endogenous BIO-IDENTICAL progesterone levels are associated with a lower overall or breast cancer incidence


Studies where the prognosis is better when the breast cancer tumour is surgically removed in the luteal phase (particularly rich in progesterone)


171. Love RR, Duc NB, Dinh NV, Shen TZ, Havighurst TC, Allred DC, DeMets DL. Mastectomy and oophorectomy by menstrual cycle phase in women with operable breast cancer. J Natl Cancer Inst 2002 May 1;94(9):662-9


Studies where the presence of mastalgia, breast cysts or uterin fibroids, conditions generally related to lower progesterone levels, is associated with an increased risk of breast cancer


III. Arguments for the use of female hormones in women (as well bio-identical as non-bio-identical): the therapy may be neutral or even protect against breast cancer

I) Studies with cancer-preventive effects of estrogen (with or without progestogen) treatment

Studies where estrogen treatment was associated with a reduction of overall cancer occurrence


Studies where estrogen therapy reduced the incidence of breast cancer

Studies where the use of estrogens before having breast cancer was associated with smaller, less aggressive tumours with more positive hormone receptors (more differentiated, less malignant tumour), less metastases, better prognosis, less recurrence

201. Magnusson C, Holmberg L, Norden T, Lindgren A, Persson I. Prognostic characteristics in breast cancers after hormone replacement therapy. Breast Cancer Res Treat. 1996;38(3):325-34 ("breast cancers occurring after treatment with HRT, especially the combined estrogen-progestin regimen, seem to have more favourable tumour features than tumours in non-treated women")

Studies where the current use of estrogens at the moment of diagnosis of breast cancer was associated with a reduced breast cancer mortality


Studies where the current use of estrogens at the moment of diagnosis of breast cancer was associated with a reduced overall mortality


Studies where estrogen therapy reduced overall mortality in women


Studies where estrogen therapy did not increase the breast cancer incidence, but increased the lifespan in women with familial risk of breast cancer

210. Sellers TA, Mink PJ, Cerhan JR, Anderson KE, Kushi LH, Folsom AR. The role of hormone replacement therapy in the risk for breast cancer and total mortality in women with a family history of breast cancer. Ann Intern Med. 1997; 127:973-80 ("HRT use in women with a family history of breast cancer is not associated with a significantly increased incidence of breast cancer but is associated with a significantly reduced total mortality rate, including overall cancer mortality")

2) Studies with cancer protective effects of ESTROGEN TREATMENT (with or without progestogen) in women who have had breast cancer

Publication where the use of corrective female hormone therapy is advised two years after a surgical cure of a hormone negative tumour

Studies where the use of HRT reduced the recurrence of breast cancer in women with previous breast cancer


Studies where the use of HRT (pill, conjugated estrogens, estradiol patch, ..) did not increase the risk of breast cancer in women with previous breast cancer


Studies where estrogen treatment of women with previous breast cancer reduced the breast cancer recurrence and increased longevity/survival time


Reviews that discuss the need of breast cancer patients to have HRT


3) Administering female hormones to women who have had breast cancer may reduce breast cancer recurrence and mortality

Studies with cancer protective effects of ESTROGEN TREATMENT (with or without progestogen) in women who have had breast cancer

Publication where the use of corrective female hormone therapy is advised two years after a surgical cure of a hormone negative tumour


Studies where the use of HRT reduced the recurrence of breast cancer in women with previous breast cancer


Studies where the use of HRT (pill, conjugated estrogens, estradiol patch, ..) did not increase the risk of breast cancer in women with previous breast cancer


Studies where estrogen treatment of women with previous breast cancer reduced the breast cancer recurrence and increased longevity/survival time


Reviews that discuss the need of breast cancer patients to have HRT


Studies where treatments with progestogens reduced the breast cancer risk


4) NO EFFECT OF HRT ON BREAST CANCER RISK

Studies with no increased breast cancer risk (or a nonsignificant lower risk) with the use of female hormone replacement therapy (conjugated estrogens or other estrogens):


247. Wingo PA, Layde PM, Lee NC, Rubin G, Ory HW. The risk of breast cancer in postmenopausal women who have used estrogen replacement therapy. JAMA. 1987 Jan 9; 257(2): 209-15


5) **Concomitant use of testosterone (which has progestative activity, but can convert into estradiol) may reduce the breast cancer risk when using female hormone therapy in women**


IV. Arguments for the use of female hormones in women with female hormone deficiency: the therapy may preserve and improve body, mind and longevity:

The importance of estrogen & progesterone for women in pre- and postmenopause is supported by evidence that the lack of these hormones is associated with psychic and physical diseases, and that their use in corrective hormone therapy reduces the severity of the associated psychic and physical diseases.

**Estrogens and psychic well-being**

**Lower estrogen levels are associated with a lower quality of life and a greater fatigue**


**Lower quality of life and fatigue improve with estrogen treatment**


64. Best NR, Rees MP, Barlow DH, Cowen PJ. Effect of estradiol implant on noradrenergic function and mood in menopausal subjects. Psychoneuroendocrinology. 1992;17(1):87-93

Vasomotor symptoms: Improvement with

**Estradiol treatment**


**Progesterone treatment**

21
Depression: the association with lower estrogen levels


Depression: the improvement with estrogen treatment


83. Best NR, Rees MP, Barlow DH, Cowen PJ. Effect of estradiol implant on noradrenergic function and mood in menopausal subjects. Psychoneuroendocrinology. 1992;17(1):87-93


Anxiety: the association with lower progesterone levels


Anxiety: the improvement with

Estrogen and progestogen treatment:


Estrogen treatment

92. Best NR, Rees MP, Barlow DH, Cowen PJ. Effect of estradiol implant on noradrenergic function and mood in menopausal subjects. Psychoneuroendocrinology. 1992;17(1):87-93


**Progestosterone treatment:**

100. Bitran D, Purdy RH, Kellogg CK. Anxiolytic effect of progesterone is associated with increases in cortical allopregnanolone and GABAA receptor function. Pharmacol Biochem Behav. 1993 Jun;45(2):423-8

**Memory loss and Alzheimer’s disease: the association with lower estrogen levels**


**Memory loss and Alzheimer’s disease: the improvement with**

**Estrogen treatment**


**Estrogen and progestogen treatment**

113. Sandstrom NJ, Williams CL. Memory retention is modulated by acute estradiol and progesterone replacement. Behav Neurosci. 2001 Apr;115(2):384-93
Sleep disorder: the association with lower estrogen levels


Sleep disorder: the improvement with estrogen treatment

117. Schiff I, Regestein Q, Tulchinsky D, Ryan KJ. Effects of estrogens on sleep and psychological state of hypogonadal women. JAMA. 1979 Nov 30;242(22):2405-4

Sleep disorder: the improvement with progesterone treatment


Loss of sexual drive, sensitivity and potency: the association with lower estrogen levels


Loss of sexual drive, sensitivity and potency: The efficacy of female hormone treatments


Estrogens and physical appearance/body composition

Sarcopenia: association with low estradiol and estrone levels


Sarcopenia: the improvement with estradiol treatment


Lean body mass: the improvement with estradiol (as well transdermal as oral) treatment

128. Sorensen MB, Rosenfalck AM, Hojgaard L, Ottesen B. Obesity and sarcopenia after menopause are reversed by sex hormone replacement therapy. Obes Res. 2001 Oct;9(10):622-6
Hirsutism: the improvement with estrogen treatment


131. Wieland RG, Zorn E. Effect of chronic combined glucocorticoid and estrogen on serum androgens and androgen binding in hirsutism. CECIL. 1979 Apr;23(4):458-60


Estrogen and age-related diseases

Hypercholesterolemia: the association with lower estrogen levels


Hypercholesterolemia: the improvement with Estrogen treatment


Progesterone treatment
Atherosclerosis: the association with lower estrogen levels


Atherosclerosis: the improvement with estrogen treatment


Arterial hypertension: the association with lower estrogen levels

159. Harrison-Bernard LM, Schulman IH, Raij L. Postovariectomy hypertension is linked to increased renal AT1 receptor and salt sensitivity. Hypertension. 2003 Dec;42(6):1157-63


Arterial hypertension: the improvement with estrogen treatment


169. Manhem K, Ahlm H, Dellborg M, Milsom I. Acute effects of transdermal estrogen therapy in postmenopausal women with coronary artery disease. Using a clinically relevant estrogen dose and concurrent antianginal therapy. Cardiology. 2000;94(2):86-90 (“resting diastolic blood pressure was significantly decreased due to estrogen”)


Cardiovascular disease: the association with lower estrogen levels


Coronary heart disease and other cardiac diseases: the improvement with estrogen treatment


175. Delyani JA, Murohara T, Nossuli TO, Lefer AM. Protection from myocardial reperfusion injury by acute administration of 17 beta-estradiol. Mol Cell Cardiol. 1996 May;28(5):1001-8


Stroke and other cerebrovascular disorders: the association with lower estrogen levels

**Stroke: the improvement with estrogen treatment**


**Obesity: the association with lower estrogen levels**


**Obesity: the improvement with estrogen treatment**

195. Sorensen MB, Rosenfalck AM, Højgaard L, Ottesen B. Obesity and sarcopenia after menopause are reversed by sex hormone replacement therapy. Obes Res. 2001 Oct;9(10):822-6
196. Tofovic SP, Dubey RK, Jackson EK. 2-Hydroxyestradiol attenuates the development of obesity, the metabolic syndrome, and vascular and renal dysfunction in obese ZSF1 rats. J Pharmacol Exp Ther. 2001 Dec;299(3):973-7

**Diabetes: the association with lower estrogen levels**


**Diabetes: the improvement with estrogen treatment**


Rheumatism: the association with lower estrogen levels


Rheumatism: the improvement with estrogen treatment


Osteoporosis: the association with lower estrogen levels

Estrogen levels


222. Khosla S, Riggs BL, Robb RA, Camp JH, Achenbach SJ, Oberg AL, Rouleau PA, Melton LJ 3rd. Relationship of volumetric bone density and structural parameters at different skeletal sites to sex steroid levels in women. J Clin Endocrinol Metab. 2005 Sep;90(9):5096-103

223. Tremolieres FA, Pouilles JM, Ribot C. Withdrawal of hormone replacement therapy is associated with significant vertebral bone loss in postmenopausal women Osteoporo Int. 2001;12(5):385-90

Estrogens and androgen levels


Osteoporosis: the improvement with Estrogen and progestin treatment

229. Sorensen MB, Rosenfalck AM, Hojgaard L, Ottesen B. Obesity and sarcopenia after menopause are reversed by sex hormone replacement therapy. Obes Res. 2001 Oct;9(10):622-6

Transdermal, intranasal or implant estradiol treatment

242. Evans SF, Davie MW. Low and conventional dose transdermal oestradiol are equally effective at preventing bone loss in spine and femur at all post-menopausal ages. Clin Endocrinol (Oxf). 1996 Jan;44(1):79-84

**Progestin (including progesterone) treatment**


**Hip fractures: the association with lower estrogen levels**


**Cancer: the association with**

**Lower estrogen levels**


**Lower progesterone levels**


Cancer: protection with estrogen treatment?


Studies with reduced breast cancer risk in women with the intake of progesterone or one of its' derivatives


Wingo PA, Layde PM, Lee NC, Rubin G, Ory HW. The risk of breast cancer in postmenopausal women who have used estrogen replacement therapy. JAMA. 1987 Jan 9; 257(2): 209-15


Studies where estrogen therapy increased the lifespan in women with familial risk of breast cancer


Studies of estrogen treatment of women with previous breast cancer: increased longevity/survival and reduced recurrence


Studies where the use of female hormone replacement therapy reduced the recurrence of breast cancer


Longevity: the association with higher progesterone levels


Longevity: the improvement with estrogen treatment


V. References on estrogen and progesterone treatment

Corrective estrogen and progestogen treatments

Estrogen treatments


Oral estradiol, conjugated estrogens


Transdermal estradiol


315. Paoletti AM, Pilia I, Nannipieri F, Bigini C, Melis GB. Comparison of pharmacokinetic profiles of a 17 beta-estradiol gel 0.6 mg/g (Gelestra) with a transdermal delivery system (Estraderm TTS 50) in postmenopausal women at steady state. Maturitas. 2001 Dec 14;40(3):203-9.


Estradiol implant


Vaginal estradiol


Transdermal estradiol treatment: dosage, site of application


Progesterone treatments

324. Stanczyk FZ. All progestins are not created equal. Steroids. 2003 Nov;68(10-13):879-90

Oral progestosterone


Oral dydrogesterone


Oral norethisterone


Vaginal progesterone


Sublingual/ buccal progesterone

Transdermal progesterone


Female hormone treatment: interferences

Estrogen treatment: interferences


Female hormone replacement: follow-up