REFERENCES ON BIO- AND NONBIO-IDENTICAL FEMALE HORMONE THERAPIES

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) et 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≥25 Kg/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 M]. 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 cance, 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 myocardial 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 the 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


