



The International Hormone Society

References of IHS statement on Bio-identical Hormones

REFERENCES ON BIO- AND NONBIO-IDENTICAL FEMALE HORMONE THERAPIES

1) 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

1. Writing group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. JAMA. 2002; 288: 321-333

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 inverted (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 \geq 25Kg/m²), 1/3 had morbid obesity (BMI \geq 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 were non-bio-identical hormones, which increased the breast cancer risk

2. Beral V. Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet. 2003 Aug 9;362(9382):419-27

(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

3. Morgan MR, Whittaker PG, Dean PD, Lenton EA, Sexton L, Cooke ID. Plasma equilin concentrations in an oophorectomized woman following ingestion of conjugated equine oestrogens (Premarin). Eur J Clin Invest. 1979 Dec;9(6):473-4
4. Bhavnani BR, Sarda IR, Woolever CA. Radioimmunoassay of plasma equilin and estrone in postmenopausal women after the administration of premarin. J Clin Endocrinol Metab. 1981 Apr;52(4):741-7
5. Utian WH, Katz M, Davey DA, Carr PJ. Effect of premenopausal castration and incremental dosages of conjugated equine estrogens on plasma follicle-stimulating hormone, luteinizing hormone, and estradiol. Am J Obstet Gynecol. 1978 Oct 1;132(3):297-302

Treatments with ethinylestradiol (the Million women study):

6. Goldzieher JW. Selected aspects of the pharmacokinetics and metabolism of ethinyl estrogens and their clinical implications. Am J Obstet Gynecol. 1990 Jul;163(1 Pt 2):318-22
7. Shenfield GM, Griffin JM. Clinical pharmacokinetics of contraceptive steroids. An update. Clin Pharmacokinet. 1991 Jan;20(1):15-37.

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)

8. Powers MS, Schenkel L, Darley PE, Good WR, Balestra JC, Place VA. Pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17-beta-estradiol: comparison with conventional oral estrogens used for hormone replacement. Am J Obstet Gynecol. 1985 Aug 15;152(8):1099-106
9. Chetkowski RJ, Meldrum DR, Steingold KA, Randle D, Lu JK, Eggena P, Hershman JM, Alkjaersig NK, Fletcher AP, Judd HL. Biologic effects of transdermal estradiol. N Engl J Med. 1986 Jun 19;314(25):1615-20

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.

10. Stumpf PG. Pharmacokinetics of estrogen. Obstet Gynecol. 1990 Apr;75(4 Suppl):9S-14S; discussion 15S-17S

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

11. Wolthers T, Hoffman DM, Nugent AG, Duncan MW, Umpleby M, Ho KK. Oral estrogen antagonizes the metabolic actions of growth hormone in growth hormone-deficient women. *Am J Physiol Endocrinol. Metab.* 2001 Dec;281(6):E1191-6
12. Paassilta M, Karjalainen A, Kervinen K, Savolainen MJ, Heikkinen J, Backstrom AC, Kesaniemi YA. Insulin-like growth factor binding protein-1 (IGFBP-1) and IGF-I during oral and transdermal estrogen replacement therapy: relation to lipoprotein(a) levels. *Atherosclerosis.* 2000 Mar;149(1):157-62
13. Janssen YJ, Helmerhorst F, Frolich M, Roelfsema F. A switch from oral (2 mg/day) to transdermal (50 µg/day) 17beta-estradiol therapy increases serum insulin-like growth factor-I levels in recombinant human growth hormone (GH)-substituted women with GH deficiency. *J Clin Endocrinol Metab.* 2000 Jan;85(1):464-7
14. Cook DM, Ludlam WH, Cook MB. Route of estrogen administration helps to determine growth hormone (GH) replacement dose in GH-deficient adults. *J Clin Endocrinol Metab.* 1999 Nov;84(11):3956-60
15. Cano A, Castelo-Branco C, Tarin JJ. Effect of menopause and different combined estradiol-progestin regimens on basal and growth hormone-releasing hormone-stimulated serum growth hormone, insulin-like growth factor-1, insulin-like growth factor binding protein (IGFBP)-1, and IGFBP-3 levels. *Fertil Steril.* 1999 Feb;71(2):261-7
16. Bellantoni MF, Vittone J, Campfield AT, Bass KM, Harman SM, Blackman MR. Effects of oral versus transdermal estrogen on the growth hormone/insulin-like growth factor I axis in younger and older postmenopausal women: a clinical research center study. *J Clin Endocrinol Metab.* 1996 Aug;81(8):2848-53
17. Ho KK, Weissberger AJ. Impact of short-term estrogen administration on growth hormone secretion and action: distinct route-dependent effects on connective and bone tissue metabolism. *J Bone Miner Res.* 1992 Jul;7(7):821-7
18. Weissberger AJ, Ho KK, Lazarus L. Contrasting effects of oral and transdermal routes of estrogen replacement therapy on 24-hour growth hormone (GH) secretion, insulin-like growth factor I, and GH-binding protein in postmenopausal women. *J Clin Endocrinol Metab.* 1991 Feb;72(2):374-81

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

19. Luboshitzky R, Shen-Orr Z, Herer P, Nave R. Urinary 6-sulfatoxymelatonin excretion in hyperandrogenic women with polycystic ovary syndrome: the effect of ethinyl estradiol-cyproterone acetate treatment. *Gynecol Endocrinol.* 2003 Dec;17(6):441-7

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

20. Rudorff KH, Herrmann J, Dieterich T, Kruskemper HL. Effect of estrogen upon thyroid metabolism. *Med Klin.* 1978 Aug 4;73(31):1109-13

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

21. Hammerstein J, Daume E, Simon A, Winkler UH, Schindler AE, Back DJ, Ward S, Neiss A. Influence of gestodene and desogestrel as components of low-dose oral contraceptives on the pharmacokinetics of ethinyl estradiol (EE2), on serum CBG and on urinary cortisol and 6 beta-hydroxycortisol. *Contraception.* 1993 Mar;47(3):263-81

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

22. Coenen CM, Thomas CM, Borm GF, Rolland R. Comparative evaluation of the androgenicity of four low-dose, fixed-combination oral contraceptives. *Int J Fertil Menopausal Stud.* 1995;40 Suppl 2:92-7
23. De Lignieres B, Basdevant A, Thomas G, Thalabard JC, Mercier-Bodard C, Conard J, Guyene TT, Mairon N, Corvol P, Guy-Grand B, et al. Biological effects of estradiol-17 beta in postmenopausal women: oral versus percutaneous administration. *J Clin Endocrinol Metab.* 1986 Mar;62(3):536-41

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

24. Heger-Mahn D, Warlimont C, Faustmann T, Gerlinger C, Klipping C. Combined ethinylestradiol/gestodene contraceptive patch: two-center, open-label study of ovulation inhibition, acceptability and safety over two cycles in female volunteers. *Eur J Contracept Reprod Health Care*. 2004 Sep;9(3):173-81))

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)

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

25. Devineni D, Skee D, Vaccaro N, Massarella J, Janssens L, LaGuardia KD, Leung AT. Pharmacokinetics and pharmacodynamics of a transdermal contraceptive patch and an oral contraceptive. *J Clin Pharmacol*. 2007 Apr;47(4):497-509.

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

26. White T, Jain JK, Stanczyk FZ. Effect of oral versus transdermal steroidal contraceptives on androgenic markers. *Am J Obstet Gynecol*. 2005 Jun;192(6):2055-9 (*patch versus oral contraceptive: 449% vs 274% increase in SHBG; -40 % vs -39% reduction of free testosterone, -26% versus - 32 % reduction in DHEA sulphate, and - 52 % versus -51% reduction in androstenediol glucuronide*)

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

27. White T, Ozel B, Jain JK, Stanczyk FZ. Effects of transdermal and oral contraceptives on estrogen-sensitive hepatic proteins. *Contraception*. 2006 Oct;74(4):293-6

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

28. Radowicki S, Skorzewska K, Szlendak K. [Safety evaluation of a transdermal contraceptive system with an oral contraceptive] *Ginekol Pol*. 2005 Nov;76(11):884-9.

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

29. Jick SS, Kaye JA, Russmann S, Jick H. Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 microg
30. of ethinyl estradiol. *Contraception*. 2006 Mar;73(3):223-8

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 ethinylestradiol to the body

31. van den Heuvel MW, van Bragt AJ, Alnabawy AK, Kaptein MC. Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. *Contraception*. 2005 Sep;72(3):168-74.

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

35. Nozaki M, Ogata R, Koera K, Hashimoto K, Nakano H. Changes in coagulation factors and fibrinolytic components of postmenopausal women receiving continuous hormone replacement therapy. *Climacteric*. 1999 Jun;2(2):124-30

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

36. Luyer MD, Khosla S, Owen WG, Miller VM. Prospective randomized study of effects of unopposed estrogen replacement therapy on markers of coagulation and inflammation in postmenopausal women. *J Clin Endocrinol Metab*. 2001 Aug;86(8):3629-34

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

37. Alkjaersig N, Fletcher AP, de Ziegler D, Steingold KA, Meldrum DR, Judd HL. Blood coagulation in postmenopausal women given estrogen treatment: comparison of transdermal and oral administration. *J Lab Clin Med*. 1988 Feb;111(2):224-8

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

38. Lobo RA, Bush T, Carr BR, Pickar JH. Effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate on plasma lipids and lipoproteins, coagulation factors, and carbohydrate metabolism. *Fertil Steril*. 2001 Jul;76(1):13-24
39. Bonduki CE, Lourenco DM, Baracat E, Haidar M, Noguti MA, da Motta EL, Lima GR. Effect of estrogen-progestin hormonal replacement therapy on plasma antithrombin III of postmenopausal women. *Acta Obstet Gynecol Scand*. 1998 Mar;77(3):330-3

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

40. Zanger D, Yang BK, Ardans J, Waclawiw MA, Csako G, Wahl LM, Cannon RO 3rd. Divergent effects of hormone therapy on serum markers of inflammation in postmenopausal women with coronary artery disease on appropriate medical management. *J Am Coll Cardiol*. 2000 Nov 15;36(6):1797-802

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

41. Oger E, Scarabin PY. Assessment of the risk for venous thromboembolism among users of hormone replacement therapy. *Drugs Aging*. 1999 Jan;14(1):55-61

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

42. Oger E, Scarabin PY. Hormone replacement therapy in menopause and the risk of cerebrovascular accident. *Ann Endocrinol (Paris)*. 1999 Sep;60(3):232-41

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

43. Prelevic GM, Kwong P, Byrne DJ, Jagroop IA, Ginsburg J, Mikhailidis DP. A cross-sectional study of the effects of hormone replacement therapy on the cardiovascular disease risk profile in healthy postmenopausal women. *Fertil Steril*. 2002 May;77(5):945-51
44. Decensi A, Omodei U, Robertson C, Bonanni B, Guerrieri-Gonzaga A, Ramazzotto F, Johansson H, Mora S, Sandri MT, Cazzaniga M, Franchi M, Pecorelli S. Effect of transdermal estradiol and oral conjugated estrogen on C-reactive protein in retinoid-placebo trial in healthy women. *Circulation*. 2002 Sep 3;106(10):1224-8

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

46. Writing group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. JAMA. 2002; 288: 321-333
47. Beral V; Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet. 2003 Aug 9;362(9382):419-27

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

48. Persson I, Thurfjell E, Bergstrom R, Holmberg L. Hormone replacement therapy and the risk of breast cancer. Nested case-control study in a cohort of Swedish women attending mammography screening. Int J Cancer 1997 Sep 4;72(5):758-61
49. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. JAMA 2000 Jan 26;283(4):485-91
50. LeBlanc ES, Viscoli CM, Henrich JB. Postmenopausal estrogen replacement therapy is associated with adverse breast. J Womens Health Gend Based Med 1999 Jul-Aug;8(6):815-23
51. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. J Natl Cancer Inst 2000 Feb 16;92(4):328-32
52. Vessey MP. Effect of endogenous and exogenous hormones on breast cancer: epidemiology. Verh Dtsch Ges Pathol 1997;81:493-

Studies that contest the validity of the above-mentioned studies

53. Creasman WT. Is there an association between hormone replacement therapy and breast cancer? J Womens Health 1998 Dec;7(10):1231-46
54. Sitruk-Ware R. Hormone therapy of menopause and risk of breast cancer. Polemics and Controversies. Presse Med 1994 Jan 8-15;23(1):38-42
55. Franceschi S. Replacement therapy in menopause and risk for breast tumors. Ann Ist Super Sanita 1997;33(2):207-11

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; cirtic: other studies have shown that estrogen replacement did not induce a greater rusk oif 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)

57. Clarkson TB. Progestogens and cardiovascular disease. A critical review. J Reprod Med. 1999 Feb;44(2 Suppl):180-4
58. Lahdenpera S, Puolakka J, Pyorala T, Luotola H, Taskinen MR. Effects of postmenopausal estrogen/progestin replacement therapy on LDL particles; comparison of transdermal and oral treatment regimens. Atherosclerosis. 1996 May;122(2):153-62
59. Wakatsuki A, Sagara Y. Effects of continuous medroxyprogesterone acetate on lipoprotein metabolism in postmenopausal women receiving estrogen. Maturitas. 1996 Aug;25(1):35-44

60. Cerquetani E, Leonardo F, Pagnotta P, Galetta P, Onorati D, Fini M, Rosano GM. Anti-ischemic effect of chronic oestrogen replacement therapy alone or in combination with medroxyprogesterone acetate in different replacement schemes. *Maturitas*. 2001 Sep 28;39(3):245-51
61. Duvernoy CS, Rattenhuber J, Seifert-Klauss V, Bengel F, Meyer C, Schwaiger M. Myocardial blood flow and flow reserve in response to short-term cyclical hormone replacement therapy in postmenopausal women. *J Gend Specif Med*. 2001;4(3):21-7,47
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
63. Mueck AO, Seeger H, Wallwiener D. Medroxyprogesterone acetate versus norethisterone: effect on estradiol-induced changes of markers for endothelial function and atherosclerotic plaque characteristics in human female coronary endothelial cell cultures. *Menopause* 2002 Jul;9(4):273-281
64. Wakatsuki A, Okatani Y, Ikenoue N, Fukaya T. Effect of medroxyprogesterone acetate on endothelium-dependent vasodilation in postmenopausal women receiving estrogen. *Circulation* 2001 Oct 9;104(15):1773-8
65. Register TC, Adams MR, Golden DL, Clarkson TB. Conjugated equine estrogens alone, but not in combination with medroxyprogesterone acetate, inhibit aortic connective tissue remodeling after plasma lipid lowering in female monkeys. *Arterioscler Thromb Vasc Biol* 1998 Jul;18(7):1164-71
66. Miyagawa K, Rosch J, Stanczyk F, Hermsmeyer K. Medroxyprogesterone interferes with ovarian steroid protection against coronary vasospasm. *Nat Med* 1997 Mar;3(3):324-7
67. Adams MR, Register TC, Golden DL, Wagner JD, Williams JK. Medroxyprogesterone acetate antagonizes inhibitory effects of conjugated equine estrogens on coronary artery atherosclerosis. *Arterioscler Thromb Vasc Biol* 1997 Jan;17(1):217-21
68. Luckas MJ, Gleeve T, Biljan MM, Buckett WM, Aird IA, Drakeley A, Kingsland CR. The effect of progestagens on the carotid artery pulsatility index in postmenopausal women on oestrogen replacement therapy. *Eur J Obstet Gynecol Reprod Biol*. 1998 Feb;76(2):221-4
69. Gorodeski GI, Yang T, Levy MN, Goldfarb J, Utian WH. Modulation of coronary vascular resistance in female rabbits by estrogen and progesterone. *J Soc Gynecol Investig*. 1998 Jul-Aug;5(4):197-202

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

70. Johnson JV, Davidson M, Archer D, Bachmann G. Postmenopausal uterine bleeding profiles with two forms of continuous combined hormone replacement therapy. *Menopause*. 2002 Jan-Feb;9(1):16-22

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

71. Miyagawa K, Vidgoff J, Hermsmeyer K. Ca²⁺ release mechanism of primate drug-induced coronary vasospasm. *Am J Physiol*. 1997 Jun;272(6 Pt 2):H2645-54
72. Minshall RD, Stanczyk FZ, Miyagawa K, Uchida B, Axthelm M, Novy M, Hermsmeyer K. Ovarian steroid protection against coronary artery hyperreactivity in rhesus monkeys. *J Clin Endocrinol Metab*. 1998 Feb;83(2):649-59
73. 3) Seeger H, Wallwiener D, Mueck AO. Effect of medroxyprogesterone acetate and norethisterone on serum-stimulated and estradiol-inhibited proliferation of human coronary artery smooth muscle cells. *Menopause*. 2001 Jan-Feb;8(1):5-9

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

74. Seeger H, Wallwiener D, Mueck AO. Effect of medroxyprogesterone acetate and norethisterone on serum-stimulated and estradiol-inhibited proliferation of human coronary artery smooth muscle cells. *Menopause*. 2001 Jan-Feb;8(1):5-9
75. Sitruk-Ware R. Progestins and cardiovascular risk markers. *Steroids*. 2000 Oct-Nov;65(10-11):651-8

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

76. Paris JM, Williams KJ, Hermsmeyer KR, Delansorne R. Nomegestrol acetate and vascular reactivity: nonhuman primate experiments. *Steroids*. 2000 Oct-Nov;65(10-11):621-7

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

77. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA*. 1998 Aug 19;280(7):605-13

78. Levesque H, Courtois H. Estrogen therapy and venous thromboembolic disease. *Rev Med Interne*. 1997;18 Suppl 6:620s-625s

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

79. Sitruk-Ware R, Plu-Bureau G. Progestins and cancer. *Gynecol Endocrinol*. 1999 Jun;13 Suppl 4:3-9
Department of Endocrinology, Hôpital Saint-Antoine, Paris.
80. Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *Int J Cancer*. 2005 Apr 10;114(3):448-54

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

81. Slater CC, Hodis HN, Mack WJ, Shoupe D, Paulson RJ, Stanczyk FZ. Markedly elevated levels of estrone sulfate after long-term oral, but not transdermal, administration of estradiol in postmenopausal women. *Menopause*. 2001 May-Jun;8(3):200-3
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
83. Notelovitz M, Johnston M, Smith S, Kitchens C. Metabolic and hormonal effects of 25-mg and 50-mg 17 beta-estradiol implants in surgically menopausal women. *Obstet Gynecol*. 1987 Nov;70(5):749-54
84. Balfour JA, Heel RC. Transdermal estradiol. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of menopausal complaints. *Drugs*. 1990 Oct;40(4):561-82

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

85. Meilahn EN. Hemostatic Factors and Ischemic Heart Disease Risk Among Postmenopausal Women. *J Thromb Thrombolysis*. 1995;1(2):125-131
86. Vehkavaara S, Silveira A, Hakala-Ala-Pietila T, Virkamaki A, Hovatta O, Hamsten A, Taskinen MR, Yki-Jarvinen H. Effects of oral and transdermal estrogen replacement therapy on markers of coagulation, fibrinolysis, inflammation and serum lipids and lipoproteins in postmenopausal women. *Thromb Haemost*. 2001 Apr;85(4):619-25
87. Tikkanen MJ. The menopause and hormone replacement therapy: lipids, lipoproteins, coagulation and fibrinolytic factors. *Maturitas*. 1996 Mar;23(2):209-16
88. Scarabin PY, Alhenc-Gelas M, Plu-Bureau G, Taisne P, Agher R, Aiach M. Effects of oral and transdermal estrogen/progesterone regimens on blood coagulation and fibrinolysis in postmenopausal women. A randomized controlled trial. *Arterioscler Thromb Vasc Biol*. 1997 Nov;17(11):3071-8
89. Akkad AA, Halligan AW, Abrams K, al-Azzawi F. Differing responses in blood pressure over 24 hours in normotensive women receiving oral or transdermal estrogen replacement therapy. *Obstet Gynecol*. 1997 Jan;89(1):97-103.
90. Nieto JJ, Cogswell D, Jesinger D, Hardiman P. Lipid effects of hormone replacement therapy with sequential transdermal 17-beta-estradiol and oral dydrogesterone. *Obstet Gynecol*. 2000 Jan;95(1):111-4
91. Perera M, Sattar N, Petrie JR, Hillier C, Small M, Connell JM, Lowe GD, Lumsden MA. The effects of transdermal estradiol in combination with oral norethisterone on lipoproteins, coagulation, and endothelial markers in postmenopausal women with type 2 diabetes: a randomized, placebo-controlled study. *J Clin Endocrinol Metab*. 2001 Mar;86(3):1140-3
92. Mueck AO, Seeger H, Lippert TH. Effect of transdermal versus oral estradiol administration on the excretion of vasoactive markers in postmenopausal women. *Gynakol Geburtshilfliche Rundsch*. 2000;40(2):61-7

93. Chen FP, Lee N, Soong YK, Huang KE. Comparison of transdermal and oral estrogen-progestin replacement therapy: effects on cardiovascular risk factors. *Menopause*. 2001 Sep-Oct;8(5):347-52

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

94. O'Sullivan AJ, Crampton LJ, Freund J, Ho KK. The route of estrogen replacement therapy confers divergent effects on substrate oxidation and body composition in postmenopausal women. *J Clin Invest*. 1998 Sep 1;102(5):1035-40

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

95. Chmouliovsky L, Habicht F, James RW, Lehmann T, Campana A, Golay A. Beneficial effect of hormone replacement therapy on weight loss in obese menopausal women. *Maturitas*. 1999 Aug 16;32(3):147-53

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.

96. Steingold KA, Matt DW, DeZiegler D, Sealey JE, Fratkin M, Reznikov S. Comparison of transdermal to oral estradiol administration on hormonal and hepatic parameters in women with premature ovarian failure. *J Clin Endocrinol Metab*. 1991 Aug;73(2):275-80

97. Van Erpecum KJ, Van Berge Henegouwen GP, Verschoor L, Stoelwinder B, Willekens FL. Different hepatobiliary effects of oral and transdermal estradiol in postmenopausal women. *Gastroenterology*. 1991 Feb;100(2):482-8

98. De Lignieres B, Basdevant A, Thomas G, Thalabard JC, Mercier-Bodard C, Conard J, Guyene TT, Mairon N, Corvol P, Guy-Grand B, et al. Biological effects of estradiol-17 beta in postmenopausal women: oral versus percutaneous administration. *J Clin Endocrinol Metab*. 1986 Mar;62(3):536-41

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

99. Lufkin EG, Ory SJ. Relative value of transdermal and oral estrogen therapy in various clinical situations. *Mayo Clin Proc*. 1994 Feb;69(2):131-5

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

100. Kerdelhue B, Jollette J. The influence of the route of administration of 17beta-estradiol, intravenous (pulsed) versus oral, upon DMBA-induced mammary tumour development in ovariectomised rats. *Breast Cancer Res Treat*. 2002 May;73(1):13-22

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

101. Hanke H, Hanke S, Ickrath O, Lange K, Bruck B, Muck AO, Seeger H, Zwirner M, Voisard R, Haasis R, Hombach V. Estradiol concentrations in premenopausal women with coronary heart disease. *Coron Artery Dis*. 1997 Aug-Sep;8(8-9):511-5

102. Bairey Merz CN, Johnson BD, Sharaf BL, Bittner V, Berga SL, Braunstein GD, Hodgson TK, Matthews KA, Pepine CJ, Reis SE, Reichek N, Rogers WJ, Pohost GM, Kelsey SF, Sopko G; WISE Study Group. Hypoestrogenemia of hypothalamic origin and coronary artery disease in premenopausal women: a report from the NHLBI-sponsored WISE study. *J Am Coll Cardiol*. 2003 Feb 5;41(3):413-9

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

103. Blumel JE, Castelo-Branco C, Leal T, Gallardo L, Saini J, Ferron S, Haya J. Effects of transdermal estrogens on endothelial function in postmenopausal women with coronary disease. *Climacteric*. 2003 Mar;6(1):38-44
104. Gerhard M, Walsh BW, Tawakol A, Haley EA, Creager SJ, Seely EW, Ganz P, Creager MA. Estradiol therapy combined with progesterone and endothelium-dependent vasodilation in postmenopausal women. *Circulation*. 1998 Sep 22;98(12):1158-63
105. Gilligan DM, Badar DM, Panza JA, Quyyumi AA, Cannon RO 3rd. Acute vascular effects of estrogen in postmenopausal women. *Circulation*. 1994 Aug;90(2):786-91

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

106. Lieberman EH, Gerhard MD, Uehata A, Walsh BW, Selwyn AP, Ganz P, Yeung AC, Creager MA. Estrogen improves endothelium-dependent, flow-mediated vasodilation in postmenopausal women. *Ann Intern Med*. 1994 Dec 15;121(12):936-41.

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

107. Gilligan DM, Quyyumi AA, Cannon RO 3rd. Effects of physiological levels of estrogen on coronary vasomotor function in postmenopausal women. *Circulation*. 1994 Jun;89(6):2545-51
108. Guetta V, Quyyumi AA, Prasad A, Panza JA, Waclawiw M, Cannon RO 3rd. The role of nitric oxide in coronary vascular effects of estrogen in postmenopausal women. *Circulation*. 1997 Nov 4;96(9):2795-801
109. Gorodeski GI, Yang T, Levy MN, Goldfarb J, Utian WH. Modulation of coronary vascular resistance in female rabbits by estrogen and progesterone. *J Soc Gynecol Investig*. 1998 Jul-Aug;5(4):197-202

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

110. Adams MR, Kaplan JR, Manuck SB, Koritnik DR, Parks JS, Wolfe MS, Clarkson TB. Inhibition of coronary artery atherosclerosis by 17-beta estradiol in ovariectomized monkeys. Lack of an effect of added progesterone. *Arteriosclerosis*. 1990 Nov-Dec;10(6):1051-7

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

111. Kim YD, Chen B, Beauregard J, Kouretas P, Thomas G, Farhat MY, Myers AK, Lees DE. 17 beta-Estradiol prevents dysfunction of canine coronary endothelium and myocardium and reperfusion arrhythmias after brief ischemia/reperfusion. *Circulation*. 1996 Dec 1;94(11):2901-8

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

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

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

113. Roque M, Heras M, Roig E, Masotti M, Rigol M, Betriu A, Balasch J, Sanz G. Short-term effects of transdermal estrogen replacement therapy on coronary vascular reactivity in postmenopausal women with angina pectoris and normal results on coronary angiograms. *J Am Coll Cardiol*. 1998 Jan;31(1):139-43
114. Albertsson PA, Emanuelsson H, Milsom I. Beneficial effect of treatment with transdermal estradiol-17-beta on exercise-induced angina and ST segment depression in syndrome X. *Int J Cardiol*. 1996 Apr 19;54(1):13-20

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

115. Walsh BA, Mullick AE, Banka CE, Rutledge JC. 17beta-estradiol acts separately on the LDL particle and artery wall to reduce LDL accumulation. *J Lipid Res*. 2000 Jan;41(1):134-41

Overview on vascular protective effects of estrogen

116. Farhat MY, Lavigne MC, Ramwell PW. The vascular protective effects of estrogen. *FASEB J*. 1996 Apr;10(5):615-24

Treatments with oral estradiol cause vasodilatation and increased distensibility of arteries

117. Angerer P, Kothny W, Stork S, von Schacky C. Hormone replacement therapy and distensibility of carotid arteries in postmenopausal women: a randomized, controlled trial. *J Am Coll Cardiol*. 2000 Nov 15;36(6):1789-96

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

118. Sumino H, Ichikawa S, Kasama S, Kumakura H, Takayama Y, Sakamaki T, Kurabayashi M. Effect of transdermal hormone replacement therapy on carotid artery wall thickness and levels of vascular inflammatory markers in postmenopausal women. *Hypertens Res.* 2005 Jul;28(7):579-84
119. Takahashi K, Tanaka E, Murakami M, Mori-Abe A, Kawagoe J, Takata K, Ohmichi M, Kurachi H. Long-term hormone replacement therapy delays the age related progression of carotid intima-media thickness in healthy postmenopausal women. *Maturitas.* 2004 Oct 15;49(2):170-7
120. Hashimoto M, Miyao M, Akishita M, Hosoi T, Toba K, Kozaki K, Yoshizumi M, Ouchi Y. Effects of long-term and reduced-dose hormone replacement therapy on endothelial function and intima-media thickness in postmenopausal women. *Menopause.* 2002 Jan-Feb;9(1):58-64

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

121. Foidart JM, Colin C, Denoo X, Desreux J, Beliard A, Fournier S, de Lignieres B. Estradiol and progesterone regulate the proliferation of human breast epithelial cells. *Fertil Steril.* 1998 May;69(5):963-9

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)

122. de Lignieres B, de Vathaire F, Fournier S, Urbinelli R, Allaert F, Le MG, Kuttann F. Combined hormone replacement therapy and risk of breast cancer in a French cohort study of 3175 women. *Climacteric.* 2002 Dec;5(4):332-40

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

123. Holmberg L, Norden T, Lindgren A, Wide L, Degerman M, Adami HO. Pre-operative oestradiol levels - relation to survival in breast cancer. *Eur J Surg Oncol.* 2001 Mar;27(2):152-6
124. MacMahon B, Cole P, Brown JB, Aoki K, Lin TM, Morgan RW, Woo NC. Urine oestrogen profiles of Asian and North American women. *Int J Cancer.* 1974 Aug 15;14(2):161-7
125. MacMahon B, Cole P, Brown JB, Aoki K, Lin TM, Morgan RW, Woo N. Oestrogen profiles of Asian and North American women. *Lancet.* 1971 Oct 23;2(7730):900-2
126. Ursin G, Wilson M, Henderson BE, Kolonel LN, Monroe K, Lee HP, Seow A, Yu MC, Stanczyk FZ, Gentschein E. Do urinary estrogen metabolites reflect the differences in breast cancer risk between Singapore Chinese and United States African-American and white women? *Cancer Res.* 2001 Apr 15;61(8):3326-9
127. Ursin G, London S, Stanczyk FZ, Gentschein E, Paganini-Hill A, Ross RK, Pike MC. Urinary 2-hydroxyestrone/16alpha-hydroxyestrone ratio and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst.* 1999 Jun 16;91(12):1067-72
128. Lemon HM. Pathophysiologic considerations in the treatment of menopausal patients withoestrogens; the role of oestriol in the prevention of mammary carcinoma. *Acta Endocrinol Suppl. (Copenh).* 1980;233:17-27
129. Vorherr H, Messer RH. Breast cancer: potentially predisposing and protecting factors. Role of pregnancy, lactation, and endocrine status. *Am J Obstet Gynecol.* 1978 Feb 1;130(3):335-58

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

130. Holmberg L, Norden T, Lindgren A, Wide L, Degerman M, Adami HO. Pre-operative oestradiol levels - relation to survival in breast cancer. *Eur J Surg Oncol* 2001 Mar;27(2):152-6

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

131. Adami HO, Bergstrom R, Holmberg L, Klareskog L, Persson I, Ponten J. The effect of female sex hormones on cancer survival. A register-based study in patients younger than 20 years at diagnosis. *JAMA*. 1990 Apr 25;263(16):2189-93
132. Adami HO, Holmberg L, Persson I. Survival and age at diagnosis in breast cancer. *N Engl J Med*. 1987 ; 316(12): 750-2

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

133. MacMahon B, Cole P, Brown JB, Aoki K, Lin TM, Morgan RW, Woo NC. Urine oestrogen profiles of Asian and North American women. *Int J Cancer*. 1974 Aug 15;14(2):161-7.
134. MacMahon B, Cole P, Brown JB, Aoki K, Lin TM, Morgan RW, Woo N. Oestrogen profiles of Asian and North American women. *Lancet*. 1971 Oct 23;2(7730):900-2.
135. Ursin G, Wilson M, Henderson BE, Kolonel LN, Monroe K, Lee HP, Seow A, Yu MC, Stanczyk FZ, Gentschein E. Do urinary estrogen metabolites reflect the differences in breast cancer risk between Singapore Chinese and United States African-American and white women? *Cancer Res*. 2001 Apr 15;61(8):3326-9.
136. Ursin G, London S, Stanczyk FZ, Gentschein E, Paganini-Hill A, Ross RK, Pike MC. Urinary 2-hydroxyestrone/16alpha-hydroxyestrone ratio and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst* 1999 Jun 16;91(12):1067-72
137. Lemon HM. Pathophysiologic considerations in the treatment of menopausal patients with oestrogens; the role of oestriol in the prevention of mammary carcinoma. *Acta Endocrinol Suppl (Copenh)* 1980;233:17-27
138. Vorherr H, Messer RH. Breast cancer: potentially predisposing and protecting factors. Role of pregnancy, lactation, and endocrine status. *Am J Obstet Gynecol* 1978 Feb 1;130(3):335-58

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

139. Salazar-Esquivel EL, Morales-Najar R, Calzada-Sanchez L. Infiltrating duct breast carcinoma: the role of estradiol and progesterone receptors. *Ginecol Obstet Mex*. 1994 Mar; 62: 85-90
140. Heise E, Gorlich M. Estradiol receptor and prognosis in human breast cancer and its metastases. *Neoplasma*. 1993;40(1):55-7
141. Nagai MA, Marques LA, Yamamoto L, Fujiyama CT, Brentani MM. Estrogen and progesterone receptor mRNA levels in primary breast cancer: association with patient survival and other clinical and tumor features. *Int J Cancer*. 1994 Nov 1; 59(3): 351-6
142. Mason BH, Holdaway IM, Mullins PR, Yee LH, Kay RG. Progesterone and estrogen receptors as prognostic variables in breast cancer. *Cancer Res* 1983 Jun;43(6):2985-90
143. Genazzani AR, Gadducci A, Gambacciani M. Controversial issues in climacteric medicine II. Hormone replacement therapy and cancer. International Menopause Society Expert Workshop. 9-12 June 2001, Operadel Duomo, Pisa, Italy. *Climacteric* 2001 Sep;4(3):181-93

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

144. Meilahn EN, De Stavola B, Allen DS, Fentiman I, Bradlow HL, Sepkovic DW, Kuller LH. Do urinary oestrogen metabolites predict breast cancer? Guernsey III cohort follow-up. *Br J Cancer*. 1998 Nov;78(9):1250-5

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

145. Seeger H, Mueck AO, Lippert TH. Effect of norethisterone acetate on estrogen metabolism in postmenopausal women. *Horm Metab Res*. 2000 Oct;32(10):436-9

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

146. Fahraeus L, Larsson-Cohn U. Oestrogens, gonadotrophins and SHBG during oral and cutaneous administration of oestradiol-17 beta to menopausal women. *Acta Endocrinol (Copenh)*. 1982 Dec;101(4):592-6

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

147. Rosano GM, Webb CM, Chierchia S, Morgani GL, Gabraele M, Sarrel PM, de Ziegler D, Collins P. Natural progesterone, but not medroxyprogesterone acetate, enhances the beneficial effect of estrogens on exercise-induced myocardial ischemia in postmenopausal women. *J Am Coll Cardiol.* 2000 Dec;36(7):2154-9

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

148. Hermsmeyer RK, Mishra RG, Pavcnik D, Uchida B, Axthelm MK, Stanczyk FZ, Burry KA, Illingworth DR, Juan C, Nordt FJ. Prevention of coronary hyperreactivity in preatherogenic menopausal rhesus monkeys by transdermal progesterone. *Arterioscler Thromb Vasc Biol.* 2004 May;24(5):955-61
149. Minshall RD, Pavcnik D, Browne DL, Hermsmeyer K. Nongenomic vasodilator action of progesterone on primate coronary arteries. *J Appl Physiol.* 2002 Feb;92(2):701-8

Treatments with intravenous progesterone increase coronary blood flow in pigs

150. Molinari C, Battaglia A, Grossini E, Mary DA, Stoker JB, Surico N, Vacca G. The effect of progesterone on coronary blood flow in anaesthetized pigs. *Exp Physiol.* 2001 Jan;86(1):101-8

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

151. Jacob MK, White RE. Diazepam, gamma-aminobutyric acid, and progesterone open K(+) channels in myocytes from coronary arteries. *Eur J Pharmacol.* 2000 Sep 8;403(3):209-19.
152. Crews JK, Khalil RA. Antagonistic effects of 17 beta-estradiol, progesterone, and testosterone on Ca²⁺ entry mechanisms of coronary vasoconstriction. *Arterioscler Thromb Vasc Biol.* 1999 Apr;19(4):1034-40
153. Jiang CW, Sarrel PM, Lindsay DC, Poole-Wilson PA, Collins P. Progesterone induces endothelium-independent relaxation of rabbit coronary artery in vitro. *Eur J Pharmacol.* 1992 Feb 11;211(2):163-7

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

154. Adams MR, Kaplan JR, Manuck SB, Koritnik DR, Parks JS, Wolfe MS, Clarkson TB. Inhibition of coronary artery atherosclerosis by 17-beta estradiol in ovariectomized monkeys. Lack of an effect of added progesterone. *Arteriosclerosis.* 1990 Nov-Dec;10(6):1051-7
155. Gerhard M, Walsh BW, Tawakol A, Haley EA, Creager SJ, Seely EW, Ganz P, Creager MA. Estradiol therapy combined with progesterone and endothelium-dependent vasodilation in postmenopausal women. *Circulation.* 1998 Sep 22;98(12):1158-63

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

156. Plu-Bureau G, Le MG, Sitruk-Ware R, Thalabard JC, Mauvais-Jarvis P. Progestogen use and decreased risk of breast cancer in a cohort study of premenopausal women with benign breast disease. *Br J Cancer* 1994 Aug;70(2):270-7
157. Plu-Bureau G, Le MG, Thalabard JC, Sitruk-Ware R, Mauvais-Jarvis P. Percutaneous progesterone use and risk of breast cancer: results from a French cohort study of premenopausal women with benign breast disease. *Cancer Detect Prev* 1999;23(4):290-6 (*the physiological increase of endogenous progesterone during luteal phase coincided with a lower proliferation of breast epithelial cells*)
158. de Lignieres B. Effects of progestogens on the postmenopausal breast. *Climacteric.* 2002 Sep;5(3):229-35

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

159. Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *Int J Cancer*. 2005 Apr 10;114(3):448-54

5-2) ENDOGENOUS BIO-IDENTICAL PROGESTERONE:

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

160. Cowan LD, Gordis L, Tonascia JA, Jones GS. Breast cancer incidence in women with a history of progesterone deficiency. *Am J Epidemiol* 1981 Aug;114(2):209-17
161. Adami HO, Bergstrom R, Holmberg L, Klareskog L, Persson I, Ponten J. The effect of female sex hormones on cancer survival. A register-based study in patients younger than 20 years at diagnosis. *JAMA*. 1990 Apr 25;263(16):2189-93
162. Adami HO, Holmberg L, Persson I. Survival and age at diagnosis in breast cancer. *N Engl J Med*. 1987 ; 316(12): 750-2
163. Mohr PE, Wang DY, Gregory WM, Richards MA, Fentiman IS. Serum progesterone and prognosis in operable breast cancer. *Br J Cancer*. 1996 Jun;73(12):1552-5
164. Badwe RA, Wang DY, Gregory WM, Fentiman IS, Chaudary MA, Smith P, Richards MA, Rubens RD. Serum progesterone at the time of surgery and survival in women with premenopausal operable breast cancer. *Eur J Cancer*. 1994;30A(4):445-8

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

165. Cooper LS, Gillett CE, Patel NK, Barnes DM, Fentiman IS. Survival of premenopausal breast carcinoma patients in relation to menstrual cycle timing of surgery and estrogen receptor/progesterone receptor status of the primary tumor. *Cancer* 1999 Nov 15;86(10):2053-8
166. Senie RT, Rosen PP, Rhodes P, Lesser ML. Timing of breast cancer excision during the menstrual cycle influences duration of disease-free survival. *Ann Intern Med* 1991 Sep 1;115(5):337-42
167. Saad Z, Vincent M, Bramwell V, Stitt L, Duff J, Girotti M, Jory T, Heathcote G, Turnbull I, Garcia B. Timing of surgery influences survival in receptor-negative as well as receptor-positive breast cancer. *Eur J Cancer* 1994;30A(9):1348-52.
168. Saad Z, Bramwell V, Duff J, Girotti M, Jory T, Heathcote G, Turnbull I, Garcia B, Stitt L. Timing of surgery in relation to the menstrual cycle in premenopausal women with operable breast cancer. *Br J Surg* 1994 Feb;81(2):217-20
169. Veronesi U, Luini A, Mariani L, Del Vecchio M, Alvez D, Andreoli C, Giacobone A, Merson M, Pacetti G, Raselli R, et al. Effect of menstrual phase on surgical treatment of breast cancer. *Lancet* 1994 Jun 18;343(8912):1545-7
170. Holli K, Isola J, Hakama M. Prognostic effect of timing of operation in relation to menstrual phase of breast cancer patient—fact or fallacy. *Br J Cancer* 1995 Jan;71(1):124-7
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
172. Goldhirsch A, Gelber RD, Castiglione M, O'Neill A, Thurlimann B, Rudenstam CM, Lindtner J, Collins J, Forbes J, Crivellari D, Coates A, Cavalli F, Simoncini E, Fey MF, Pagani O, Price K, Senn HJ. Menstrual cycle and timing of breast surgery in premenopausal node-positive breast cancer: results of the International Breast Cancer Study Group (IBCSG) Trial VI. *Ann Oncol* 1997 Aug;8(8):751-6
173. Vanek VW, Kadivar TF, Bourguet CC. Correlation of menstrual cycle at time of breast cancer surgery to disease-free and overall survival. *South Med J* 1997 Aug;90(8):780-8
174. Lemon HM, Rodriguez-Sierra JF. Timing of breast cancer surgery during the luteal menstrual phase may improve prognosis. *Nebr Med J* 1996 Mar;81(3):73-8
175. Badwe RA, Mitra I, Havaladar R. Timing of surgery during the menstrual cycle and prognosis of breast cancer. *J Biosci* 2000 Mar;25(1):113-2
176. Mangia A, De Lena M, Barletta A, Marzullo F, Attolico M, Stea B, Petroni S, Labriola A, Cellamare G, Digiesi G, Altieri R, Schittulli F, Paradiso A. Timing of breast cancer surgery within the menstrual cycle: tumor proliferative activity, receptor status and short-term clinical outcome. *J Exp Clin Cancer Res* 1998 Sep;17(3):317-23
177. Tsuchiya A, Furukawa H, Kanno M, Kimijima I, Abe R. Lack of the relationship between menstrual status and timing of surgery in survival of premenopausal patients with breast cancer. *Fukushima J Med Sci*. 1996 Dec;42(1-2):11-6.
178. Jager W, Sauerbrei W. Effect of timing of surgery during the menstrual cycle of premenopausal breast cancer patients. *Breast Cancer Res Treat* 1995 Jun;34(3):279-87

179. Zhang B, Shao Y, Wang C. Prognosis of patients with breast cancer related to the timing of operation during menstrual cycle: a report of 218 patients. *Zhonghua Zhong Liu Za Zhi* 1996 May;18(3):203-7
180. Milella M, Nistico C, Ferraresi V, Vaccaro A, Fabi A, D'Ottavio AM, Botti C, Giannarelli D, Lopez M, Cortesi E, Foggi CM, Antimi M, Terzoli E, Cognetti F, Papaldo P. Breast cancer and timing of surgery during menstrual cycle: a 5-year analysis of 248 premenopausal women. *Breast Cancer Res Treat* 1999 Jun;55(3):259-6

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

181. Plu-Bureau G, Thalabard JC, Sitruk-Ware R, Asselain B, Mauvais-Jarvis P. Cyclical mastalgia as a marker of breast cancer susceptibility: results of a case-control study among French women. *Br J Cancer* 1992 Jun;65(6):945-9
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