

## **Reviews: Transdermal estradiol and progesterone restoration does not carry the same risks as CEE-MPA (PremPro®)**

L'Hermite M. HRT optimization, using transdermal estradiol plus micronized progesterone, a safer HRT. *Climacteric*. 2013 Aug;16 Suppl 1:44-53.

***...Natural, 'body-identical' progesterone...appears to be the optimal progestogen in terms of cardiovascular effects, blood pressure, VTE, probably stroke and even breast cancer...***

Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ*. 2008 May 31;336(7655):1227-31.

***...The combination of oral oestrogen and thrombogenic mutations or obesity further enhanced the risk of venous thromboembolism, whereas transdermal oestrogen did not seem to confer additional risk in women at high risk of venous thromboembolism.***

Caufriez A. Hormonal replacement therapy (HRT) in postmenopause: a reappraisal. *Ann Endocrinol (Paris)*. 2007 Sep;68(4):241-50.

***...The combination of transdermal estradiol+micronized progesterone appears to be effective and relatively safe if elementary precautions are taken, and seems to be presently the best choice for HRT in most postmenopausal women.***

Holtorf K. The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? *Postgrad Med*. 2009 Jan;121(1):73-85.

***...Physiological data and clinical outcomes demonstrate that bioidentical hormones are associated with lower risks, including the risk of breast cancer and cardiovascular disease, and are more efficacious than their synthetic and animal-derived counterparts.***

Simon JA. What's new in hormone replacement therapy: focus on transdermal estradiol and micronized progesterone. *Climacteric*. 2012 Apr;15 Suppl 1:3-10.

***...Unlike oral estrogens, transdermal estradiol has been shown not to increase the risk of VTE, or stroke (doses  $\leq$  50  $\mu$ g), and to confer a significantly lower risk for gallbladder disease. Unlike some progestogens, progesterone is also not associated with an increased risk of VTE, or with an increased risk of breast cancer.***

Ribot C, Tremollieres F. [Hormone replacement therapy in postmenopausal women: all the treatments are not the same.] *Gynecol Obstet Fertil*. 2007 May;35(5):388-397.

***...the bio-identicals hormones, estradiol 17beta and progesterone, have intrinsic properties which can lead to tangible differences in therapeutic results...cardiovascular and breast cancer risks might be lower with bio-identical hormones than with other therapeutic schemes.***

Mueck AO. Postmenopausal hormone replacement therapy and cardiovascular disease: the value of transdermal estradiol and micronized progesterone. *Climacteric*. 2012 Apr;15 Suppl 1:11-7.

***...unlike oral estrogens, transdermal estradiol does not increase the risk of venous thromboembolism...and does not increase the risk of stroke. It is cardioprotective, significantly reducing the incidence of myocardial infarction...Micronized progesterone has also been shown not to increase the risk of venous thromboembolism.***

## **Studies: Transdermal estradiol and progesterone do not increase thrombotic risk (DVT's, heart attacks or strokes)**

Canonico M, Fournier A, Carcaillon L, Olié V, et al. Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism: results from the E3N cohort study. *Arterioscler Thromb Vasc Biol*. 2010 Feb;30(2):340-5.

***...odds ratios (ORs) for VTE in current users of oral and transdermal estrogen compared with nonusers were 4.2 and 0.9, respectively. There was no significant association of VTE with micronized progesterone (OR: 0.7).***

Canonico M, Oger E, Plu-Bureau G, Conard J, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation*. 2007 Feb 20;115(7):840-5.

***...Oral but not transdermal estrogen is associated with an increased VTE risk...micronized progesterone and pregnane derivatives appear safe with respect to thrombotic risk.***

Laliberté F, Dea K, Duh MS, Kahler KH, et al., Does the route of administration for estrogen hormone therapy impact the risk of venous thromboembolism? Estradiol transdermal system versus oral estrogen-only hormone therapy. *Menopause*. 2011 Oct;18(10):1052-9.

***... participants receiving an estradiol transdermal system have a significantly lower incidence of venous thromboembolism than do participants receiving oral estrogen-only hormone therapy.***

Løkkegaard E, Andreasen AH, Jacobsen RK, Nielsen LH, et al., Hormone therapy and risk of myocardial infarction: a national register study. *Eur Heart J*. 2008 Nov;29(21):2660-8.

***...Significantly lower risk (of MI) was found with dermal route (transdermal estradiol - RR 0.6) compared to no HRT (RR 1.0) or oral unopposed oestrogen therapy (RR 1.0)... (Transdermal estradiol reduced MI risk by 40%).***

Scarabin PY, Alhenc-Gelas M, Plu-Bureau G, Taisne P, et al. 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

***...oral estrogen/progesterone replacement therapy may result in coagulation activation...whereas opposed transdermal estrogen appears without any substantial effects on hemostasis.***

Shufelt CL, Merz CN, Prentice RL, Pettinger MB, et al., Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the Women's Health Initiative Observational Study. *Menopause*. 2014 Mar;21(3):260-6.

***... oral estradiol was associated with lower hazard ratios (HRs) for stroke than oral conjugated equine estrogens (HR, 0.64)... transdermal estradiol was associated with a lower risk of CHD compared with oral CEE (HR, 0.63)***

Sweetland S, Beral V, Balkwill A, Liu B, et al. The Million Women Study Collaborators. Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study. *J Thromb Haemost*. 2012 Nov;10(11):2277-86.

***..risk was significantly greater for oral estrogen-progestin than oral estrogen-only therapy (RR=2.07 versus 1.42), with no increased risk with transdermal estrogen-only therapy (RR=0.82).***

Lowe GD, Upton MN, Rumley A, McConnachie A, O'Reilly DS, Watt GC. Different effects of oral and transdermal hormone replacement therapies on factor IX, APC resistance, t-PA, PAI and C-reactive protein--a cross-sectional population survey. *Thromb Haemost*. 2001 Aug;86(2):550-6.

***...Oral HRT use was associated with increased plasma levels of Factor IX, activated protein C (APC) resistance, and CRP...The foregoing associations were not observed in users of transdermal HRT;...***

## **Studies and Reviews: Estradiol-progesterone restoration does not increase proliferation in the breast or breast cancer incidence.**

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

***...progesterone does not have a detrimental effect on breast tissue...medroxyprogesterone acetate and 19-Nortestosterone-derivatives are endowed with some non-progesterone-like effects, which can potentiate the proliferative action of estrogens.***

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

***...Among users of EP therapy containing a synthetic progestin, the odds ratio for breast cancer was 1.57 for progesterone-derived and 3.35 (1.07-10.4) for testosterone-derived progestagens. No increased risk was apparent among EP therapy users treated with natural micronized progesterone.***

Espié M, Daures JP, Chevallier T, Mares P, Micheletti MC, De Reilhac P. Breast cancer incidence and hormone replacement therapy: results from the MISSION study, prospective phase. *Gynecol Endocrinol.* 2007 Jul;23(7):391-7.

***...Breast cancer incidence in the exposed group...estradiol alone 0.28%; estradiol + progesterone 0.40%; estradiol + synthetic progestin 0.94%.***

Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. *Breast Cancer Res Treat.* 2008 Jan;107(1):103-11.

***...the relative risk was 1.00 for estrogen-progesterone,...and 1.69 for estrogen with other progestagens.***

Gompel A. Micronized progesterone and its impact on the endometrium and breast vs. progestogens. *Climacteric.* 2012 Apr;15 Suppl 1:18-25.

***...However, all progestogens are not equivalent in their effects on the breast and breast cancer risk. Micronized progesterone does not increase cell proliferation in breast tissue in postmenopausal women compared with synthetic medroxyprogesterone acetate (MPA).***

Murkes D, Lalitkumar PG, Leifland K, Lundström E, Söderqvist G. Percutaneous estradiol/oral micronized progesterone has less-adverse effects and different gene regulations than oral conjugated equine estrogens/medroxyprogesterone acetate in the breasts of healthy women in vivo. *Gynecol Endocrinol.* 2012 Oct;28 Suppl 2:12-5.

***...estradiol (E2) gel 1.5 mg and oral micronized progesterone (P) 200 mg/day...did not significantly increase breast epithelial proliferation...oral conjugated equine estrogens (CEE) 0.625 mg and oral medroxyprogesterone acetate (MPA)...significantly increased proliferation at both the cell level and at the mRNA level, and significantly enhanced mammographic breast density,...CEE/MPA affected around 2,500 genes compared with just 600 affected by E2/P.***

Modena MG, Sismondi P, et al. New evidence regarding hormone replacement therapies is urgently required transdermal postmenopausal hormone therapy differs from oral hormone therapy in risks and benefits. *Maturitas.* 2005 Sep 16;52(1):1-10.

***...The hypothesis of progesterone and some progesterone-like progestins decreasing the proliferative effect of estradiol in the postmenopausal breast remains highly plausible...***

## **Studies and Reviews: Testosterone restoration in women does not increase cardiovascular or breast cancer risks.**

Braunstein GD. Safety of testosterone treatment in postmenopausal women. *Fertil Steril*. 2007 Jul;88(1):1-17.

*...Except for hirsutism and acne, the therapeutic administration of T in physiologic doses is safe for up to several years.*

Dimitrakakis C, Zhou J, Wang J, Belanger A, et al., A physiologic role for testosterone in limiting estrogenic stimulation of the breast. *Menopause*. 2003 Jul-Aug;10(4):292-8.

*...These findings suggest that treatment with a balanced formulation including all ovarian hormones may prevent or reduce estrogenic cancer risk in the treatment of girls and women with ovarian failure.*

Dimitrakakis C, Jones RA, Liu A, Bondy CA. Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. *Menopause*. 2004 Sep-Oct;11(5):531-5.

*... the addition of testosterone to conventional hormone therapy for postmenopausal women does not increase and may indeed reduce the hormone therapy-associated breast cancer risk...*

Rudenko L.V., Ramazanov Y.I., Kalinchenko S.Y. Estimation of prolonged androgen therapy safety in patients with female-male transsexualism. *The Aging Male*, March 2006; 9(1): 1–70

*...Results showed safety of the extended androgen therapy regarding cardio-vascular system, carbohydrate metabolism and impact on hepatic function.*

Somboonporn W, Davis SR; National Health and Medical Research Council. Testosterone effects on the breast: implications for testosterone therapy for women. *Endocr Rev*. 2004 Jun;25(3):374-88.

*...Based on such simulations, inclusion of testosterone in postmenopausal estrogen-progestin regimens has the potential to ameliorate the stimulating effects of combined estrogen-progestin on the breast.*

Somboonporn W, Davis SR. Postmenopausal testosterone therapy and breast cancer risk. *Maturitas*. 2004 Dec 10;49(4):267-75.

*...Available data indicate the inclusion of testosterone in estrogen-progestin regimens has the potential to ameliorate the stimulating effects of hormones on the breast.*

Traish AM, Gooren LJ. Safety of physiological testosterone therapy in women: lessons from female-to-male transsexuals (FMT) treated with pharmacological testosterone therapy. *J Sex Med*. 2010 Nov;7(11):3758-64.

*...No significant serious adverse effects were reported in FMTs treated with pharmacological doses of T...*

Huang G, Tang E, Aakil A, Anderson S, Jara H, Davda M, Stroh H, Trivison TG, Bhasin S, Basaria S. Testosterone dose-response relationships with cardiovascular risk markers in androgen-deficient women: a randomized, placebo-controlled trial. *J Clin Endocrinol Metab*. 2014 Jul;99(7):E1287-93.

*...Short-term testosterone administration over a wide range of doses for 24 weeks in women with low T levels was not associated with worsening of cardiovascular risk markers.*

Shufelt CL, Braunstein GD. Testosterone and the breast. *Menopause Int*. 2008 Sep;14(3):117-22.

*...Thus, the preponderance of data suggests that testosterone use in females is not associated with an increased risk of breast carcinoma.*