Miscellaneous Research Abstracts

Prevention of mammary carcinogenesis by short-term estrogen and progestin treatments.

Rajkumar L, Guzman RC, Yang J, Thordarson G, Talamantes F, Nandi S
Breast Cancer Research. 2004; 6(1): R31-R37

It is universally observed in women of all ethnicities that a full-term pregnancy has a protective effect. This phenomenon is not limited to humans, having also been observed in rats and mice. The aim of this study was to examine the effect of various natural and/or synthetic estrogens and progestins at different doses and durations on the incidence of mammary cancer in mice following exposure to N-methyl-N-nitrosourea, a known carcinogen. Estriol, which is known to increase during pregnancy, was tested alone and in combination with progesterone. Synthetic estrogens and progestins in various combinations were also tested. All hormone treatments were given 2 weeks after administration of the carcinogen. Researchers found that treatment with 30mg estriol and 30mg progesterone for a 3-week period significantly reduced the incidence of mammary cancer.

The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy?

Holtorf K.
Postgraduate Medicine. 2009 Jan, 121 (1): 73-85

This paper evaluates evidence from published studies comparing bio-identical hormones with commonly used synthetic hormones for clinical efficacy, physiologic actions on breast tissue and cardiovascular disease. Several studies were found that included patients using HRT, both synthetic and bio-identical. These studies reported women experiencing greater satisfaction, fewer side effects and improved quality of life when switched from synthetic progestins to progesterone replacement. In one particular survey, patient satisfaction, quality of life, and somatic and psychological problems (i.e. anxiety, depression, sleep problems) were measured in menopausal women either on HRT with medroxyprogesterone (MPA) or HRT with progesterone. Overall, 65% of women felt HRT with progesterone was better and there were measured reductions in sleep problems, anxiety, somatic symptoms, menstrual bleeding, cognitive difficulties and improvements in sexual function. Synthetic progestins and progesterone were also found to have differences in their molecular and pharmacological effects on breast tissue, with synthetic progestins demonstrating procarcinogenic effects compared with the anticarcinogenic properties of progesterone.

A comprehensive review of the safety and efficacy of bioidentical hormones for the management of menopause and related health risks. Bioidentical hormones review.

Moskowitz D.
Alternative Medicine Review. 2006 Sep, 11 (3): 208-223

The purpose of this article was to comprehensively review and evaluate the safety and efficacy of bio-identical hormones in the management of menopausal symptoms. Some of the studies reviewed involved both bio-identical estrogens and progesterone and they were found to be effective in tackling menopausal symptoms and were associated with a reduced risk of blood clots compared to synthetic hormone therapy. One study involving 3,175 post-menopausal women predominantly using natural hormone therapy found there was no increased risk of breast cancer compared with conventional HRT. A second cohort study with 54,548 post-menopausal women found the risk of breast cancer to be significantly greater with HRT involving synthetic hormones versus HRT with bio-identical hormones. These large cohort studies assessing the safety of bio-identical hormones provide significant evidence to support the safety of bio-identical HRT with respect to breast tissue.

Risk of breast cancer by type of menopausal hormone therapy: a case-control study among post-menopausal women in France.

Cordina-Duverger E, Truong T, Anger A, et al.
PLoS ONE. 2013 Nov, 8(11):e78016

This population-based case-controlled study aimed to determine the effects of specific formulations of estrogen and progesterone (EP) hormone therapy on the risk of breast cancer in menopausal women. The study found that the risk of breast cancer differed depending on the type of progestogen administered. There was no apparent increased risk among EP therapy when the women were being treated with natural micronised progesterone. Tibolone, a synthetic steroid hormone with both estrogenic and progestogenic properties was also involved in this study, and was found to increase the risk of breast cancer compared with any EP therapy. It was also strongly associated with estrogen-receptor and progesterone-receptor positive tumours.

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.

Murkes D, Lalitkumar PG, Leifland K, Lundstrom E, Soderqvist G.
Gynecological Endocrinology. 2012 Oct;28(Suppl. 2): 12–5.

In this prospective clinical study, gene expression analysis of healthy post-menopausal women indicated that the genes which encode Ki-67, a cellular marker for proliferation, and progesterone receptor B mRNA are differentially expressed in women taking bio-identical or natural estrogen HRT. Two 28-day cycles of daily estradiol gel (1.5mg) and oral micronized progesterone (200mg) on days 14-28 did not significantly increase breast epithelial proliferation at the cellular level nor the mRNA level. However, daily oral conjugated equine estrogens (CEE) (0.625mg) and oral medroxyprogesterone acetate (MPA) (5mg on days 14-28) significantly increased proliferation at both the cellular and mRNA level. Furthermore, CEE + MPA was found to significantly enhance mammographic breast density, an important risk factor for breast cancer. This finding suggests that hormone therapy using natural estrogens effects a smaller number of genes and has less adverse effects on the normal breast in vivo than synthetic hormone therapy.

Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study.

Fournier A, Berrino F, Clavel-Chapelon F.
Breast Cancer Research and Treatment. 2008 Jan; 107(1):103–11.

One aspect of this study was to assess the relative risk of invasive breast cancer according to route of estrogen administration and the type of progestogen, versus absence of HRT. The study found that for any given route of estrogen administration (oral or transdermal), the relative risk varied significantly between the different progestogens. Estrogen + progesterone and estrogen + dydrogesterone were associated with “no”, “slight” or “non-significant” increases in risk. All other combinations of estrogen + progestogen were associated with an increased risk in invasive breast cancer, with most increases being statistically significant.

Could transdermal estradiol + progesterone be a safer postmenopausal HRT? A review.

L’Hermite M, Simoncini R, Fuller S, Genazzani AR.
Maturitas. 2008 Jul-Aug; 60(3-4): 185-201

This paper reviewed the safety of hormones administered by non-oral routes for the clinical management of post-menopausal women. After reviewing research, the authors concluded that non-oral administration of estrogens minimised the hepatic induction of clotting factors and other proteins which are associated with the first-pass effect. Non-oral estrogens were also associated with cardiovascular benefits; for example, the risk of developing deep vein

thrombosis or pulmonary thromboembolism was found to be negligible. In addition to these findings, the review found evidence to show that natural progesterone displays a favourable action on vasculature and the brain when compared to synthetic progestins.

Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study.

Canonico M, Oger E, Plu-Bureau G, et al.
Circulation. 2007 Feb; 115(7):840–5

Canonico et al. performed a multicentre case-control study involving post-menopausal women aged 45 -70 years old to assess the impact of the route of estrogen administration on venous thromboembolism (VTE) risk. The collected data confirmed that oral estrogen therapy significantly increases the VTE risk in post-menopausal women, whereas there was no associated risk with transdermal estrogen. Additionally, the use of micronised progesterone was found to be safe with respect to thrombotic risk. This study emphasises the importance of considering the route of hormone administration, enabling women and healthcare practitioners to be better informed in the management of menopausal symptoms.

What's new in hormone replacement therapy: focus on transdermal estradiol and micronized progesterone.

Simon JA.
Climacteric 2012;15(1): 3-10.

The use of transdermal estradiol and micronised progesterone for the management of menopausal women with a personal or family history of venous thromboembolism (VTE) has been supported in guidelines from the North American Menopause Society, the Endocrine Society, the International Menopause Society and the European Menopause and Andropause Society. Transdermal estradiol has been shown to not increase the risk of VTE or stroke when administered at doses ≤ 50µg. Furthermore, there is also a significantly lower risk for gallbladder disease with transdermal delivery compared with oral estrogens. Micronised progesterone is not associated with an increased risk of VTE nor with breast cancer which is contrary to the data relating to the use of some progestogens.

The Effectiveness of Sublingual and Topical Compounded Bioidentical Hormone Replacement Therapy in Postmenopausal Women: An Observational Cohort Study.

Ruiz AD & Daniels KR.
International Journal of Pharmaceutical Compounding 2014;18(1): 70-77.

The aim of this prospective, observational study was to determine the effectiveness of sublingual and topical compounded bio-identical hormone replacement therapy (BHRT) in treating vasomotor, mood and other quality of life symptoms in post-menopausal women. The women in the study were allocated to receive sublingual or topical BHRT, with 100% of the sublingual group and 99% of the topical group receiving progesterone as part of their BHRT regimen. Overall, the researchers found that women who received BHRT in a sublingual form experienced statistically significant reductions in menopausal symptoms, mood symptoms, vasomotor symptoms, sleep disturbances, memory loss, fatigue and loss of libido at one to three-month follow-ups compared to baseline. The women in the topical BHRT group experienced some improvements in moderate to severe menopausal symptoms, and this type of therapy resulted in statistically significant reductions in mood swings, irritability and night sweats only.

A study to look at hormonal absorption of progesterone cream used in conjunction with transdermal estrogen.

Vashisht A, Wadsworth F, Carey A, Carey B, Studd J.
Gynecological Endrocrinology 2005;21(2): 101-105.
The aim of this study was to assess the systemic absorption of a daily dose of natural progesterone cream administered in conjunction with transdermal estrogen as part of continuous combined hormone replacement therapy. Each patient was supplied with clearly labelled separate containers of Progestelle® (6% progesterone cream) and estradiol gel, Sandrena® sachets, which amounted to a total daily 40mg dose of progesterone and 1mg of estradiol over 48 weeks. Assessments were conducted at 12-week intervals throughout the study to determine any improvements to menopausal symptoms. After 24 and 48 weeks, there were highly significant reductions in anxiety, depression, vasomotor symptoms and lipid problems compared with baseline. There was also a statistically significant reduction in anxiety symptoms after the first 24 weeks. Plasma levels of progesterone and estradiol were measured in women who completed the study and these showed significant increases in both hormone levels from baseline levels at each time interval.

Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis.
Canonico M, Plu-Bureau G, Lowe GDO, Scarabin P. British Medical Journal 2008;336:1227-31.
Canonico et al. carried out a systematic review and meta-analysis of both observational studies and randomised clinical trials to assess the overall risk of venous thromboembolism (VTE) in relation to hormone replacement therapy (HRT). The principal findings from the meta-analysis were that current use of oral estrogen increases the risk of VTE by 2-3 times and the elevation is much higher within the first year of treatment with HRT. In addition, a combination of oral estrogen and increased body-mass index was found to further increase in risk of VTE. The risk of VTE did not appear to be different when comparing unopposed and opposed oral estrogen therapy. The combined analysis of observational studies indicated that was no significant increase in the risk of VTE with the use of transdermal estrogen.

Hormone therapy and risk of cardiovascular outcomes and mortality in women treated with statins.
Berglind IA, Andersen M, Citarella A, et al.
Menopause 2015;22(4):369–76
The aim of this study was to assess the effects of hormone replacement therapy on the risk of cardiovascular and all-cause mortality in women aged between 40 -74 who were receiving treatment with statins. A total of 40,958 statin users (2,862 hormone therapy users and 38,096 non-users) were followed for a mean of 4 years. Overall, the study found that among hormone therapy users, there were 5 cardiovascular deaths per 10,000 person-years; the corresponding rate for non-users was 18. The all-cause mortality rates were 33 (HT-users) and 87 (non-users). The authors concluded that hormone therapy is associated with a reduce risk of all-cause mortality in women who are receiving statins.

Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomized trial.
Schierbeck LL, Rejnmark L, Tofteng CL, et al.
BMJ 2012;345:e6409
This aim of this open label, randomised, controlled trial was to investigate the long term effect of hormone replacement therapy on cardiovascular outcomes in 1,006 women who were recently menopausal. The women were randomised to receive either the control or were assigned to a treatment group; women received triphasic estradiol and norethisterone acetate, and for women who had undergone a hysterectomy 2mg estradiol daily was administered. The primary endpoint in this study was a composite of death, admission to hospital for heart failure and myocardial infarction. After 10 years of intervention, 16 women in the treatment group experienced this primary composite endpoint compared with 33 in

the control group. This finding indicates that the women receiving HRT had a significantly reduced risk of mortality, heart failure or myocardial infarction without any apparent increase in the risk of cancer, venous thromboembolism, or stroke.

Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study.

Renoux C, Dell'aniello S, Garbe E, et al.
BMJ 2010;340:c2519

The aim of this population based, nested, case-control study was to determine the risk of stroke associated with oral and transdermal administration of hormone replacement therapy. The study matched 15,710 cases of stroke to 59,958 controls. The types of HRT were categorised into estrogens only, estrogens plus progestogens, progestogen only and tibolone. These treatments were further subcategorised according to delivery method (oral versus transdermal) and dose (high versus low). Overall, the study found that there was no increase in the risk of stroke with the use of low estrogen dose patches compared to no use. However, there was a significant increase in risk associated with high dose transdermal estrogen patches. Users of both low and high dose oral HRT had a significantly increased risk of stroke than non-users.