FUNCTIONAL AND PERSONALISED HORMONE RESTORATION THERAPY: THE FUNDAMENTALS

EXCERPT FROM PROGRAM:

Appendix C: Evidence-based Medicine Used in Hormone Restoration Therapy

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This section highlights a series of research abstracts that clarify misconceptions, provides evidence for program content as well as simply providing a learning experience for the reader. Sub-sections include:

- Risk of Thromboembolism
- Breast Cancer and Hormone therapy
- Progesterone Therapy
- Estrogen Therapy
- Thyroid
- Androgen Therapy – Testosterone
- Androgen therapy – DHEA
- Cortisol

Risk of Thromboembolism

- **Canonico, M., et al. "Hormone Therapy and Venous Thromboembolism Among Postmenopausal Women: Impact of the Route of Estrogen Administration and Progestogens: The ESTHER Study"** ***Circulation.*** **February 20, 2007. Vol 115. P 840-845.**

"Oral but not transdermal estrogen is associated with an increased VTE risk. In addition, our data suggest that norpregnane derivatives may be thrombogenic, whereas micronized progesterone and pregnane derivatives appear safe with respect to thrombotic risk.

- **Eisenberger, A. & Westhoff, C. (2014). Hormone replacement therapy and venous thromboembolism.** ***The Journal of Steroid Biochemistry and Molecular Biology,*** **142, 76-82.**

"The risk of venous thromboembolism appears to be greatest soon after the initiation of HRT and returns to the baseline level of risk of non-HRT users after discontinuation."

"Retrospective analyses suggest that transdermal HRT is not as prothrombotic as oral HRT, though this has not been evaluated in randomised clinical trials."

"Increasing age and weight further promote HRT's venous thromboembolism risk."

- **L'Hermite, M. (2013). HRT optimisation, using transdermal estradiol plus micronised progesterone, a safer HRT.** ***Climacteric, 16,*** **44–53.**

"The venous thromboembolism risk is associated with oral rather than transdermal estrogen administration and there is increasing evidence that risk is greater in combination with certain progestogens such as norpregnane derivatives and medroxyprogesterone acetate."

"In 'high-risk' individuals who require HRT, transdermal preparation should be used and is a progestogen is required, suitable options might include micronised progesterone or dydrogesterone."

- **Schmidt, John W. "Hormone replacement therapy in menopausal women: Past problems and future possibilities" *Gynecological Endocrinology,* October 2006; 22(10): 564-577.**

"Oral administration of conjugated equine estrogens (CEE) with and without the synthetic progestin medroxyprogesterone acetate (MPA) in postmenopausal women is associated with side-effects that include increased risk of stroke and breast cancer. The current evidence that transdermal administration of estradiol may provide a safer alternative to orally administered CEE is reviewed. Transdermally administered estradiol has been shown to be an efficacious treatment for hot flushes possibly without the increase in blood clotting that is associated with administration of oral CEE. Further, natural progesterone may have a more beneficial spectrum of physiological effects than synthetic progestins. The substantial differences between CEE compared with estradiol and estriol, as well as the differences between synthetic MPA and natural progesterone, are detailed. Estriol is an increasingly popular alternative hormone therapy used for menopausal symptoms. There is evidence that estriol, by binding preferentially to estrogen receptor-B, may inhibit some of the unwanted effects of estradiol. "

"Relief of hot flushes in postmenopausal women can usually be achieved by maintaining serum estradiol levels at 40-50 pg/ml, the lowest level of estradiol that is expected to be seen in a typical menstrual cycle."

"The rapid metabolism by the liver and the hydrophobic nature of sex steroid hormones suggests that topical administration should be carefully considered as a viable route of administration."

"There are studies that indicate progesterone may have fewer side-effects than synthetic progestins."

"Several lines of investigation have suggested that estriol might be able to act in a complementary way with ER alpha-preferring estrogens to limit estrogen-induced cell proliferation and, possible, carcinogenesis."

- **Stegeman, B.H. et al. (2013). Different combined oral contraceptives and the risk of venous thrombosis: Systemic review and network meta-analysis. *British Medical Journal, 347,* f5298**

"Users of combined oral contraceptives with third generation progestogens have a higher risk of venous thrombosis than those using second generation progestogens. "

- **Vinogradova, Y., Coupland, C., & Hippisley-Cox, J. Use of hormone replacement therapy and risk of venous thromboembolism: Nested case-control studies using the QResearch and CPRD databases. *BMJ, 2019,* 1-14.**

"Oral [HRT] was associated with a significantly increased risk of venous thromboembolism compared with no exposure (adjusted odds ratio of 1.58, 95% confidence interval 1.52 to 1.64), for both estrogen only preparations (1.40, 1.32 to 1.48) and combined preparations (1.73, 1.65 to 1.81). Estradiol had a lower risk than conjugated equine estrogen for estrogen only preparation (0.85, 0.76 to 0.95) and combined preparations (0.83, 0.76 to 0.91). Compared with no exposure, conjugated equine estrogen with medroxyprogesterone acetate has the highest risk (2.10, 1.92 to 2.31), and estradiol with dydrogesterone had the lowest risk (1.18, 0.98 to 1.42). Transdermal preparations were not associated with risk of venous thromboembolism, which was consistent for different regimens (overall adjusted odds ratio 0.93, 95% confidence intervak 0.87 to 1.01."

Risk of Breast Cancer

- **Anderson, G.L. et al. (2012). Conjugated equine estrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: Extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. *Lancet Oncology, 13,* 476–486.**

"Elevated concentrations of endogenous estrogen have been consistently associated with increased risk of breast cancer. Exogenous estrogen use has also been associated with higher breast cancer incidence in many but not all observational studies, especially in leaner women and those receiving estrogen long term. Estrogen use has been linked to hormone-receptor positive and early stage disease, suggesting a better prognosis, although associations with breast cancer mortality are mixed."

"Between 1993 and 1998, the WHI enrolled 10739 postmenopausal women from 40 US clinical centres into a randomised, double-masked, placebo-controlled trial. Women aged 50-79 who had undergone hysterectomy and had expected 3-year survival and mammography clearance were randomly allocated by a computerised, permuted block algorithm, stratified by age group and centre, to receive oral conjugated equine estrogen (0.625 mg per day; n=5310) or matched placebo (n=5429)."

"After a median follow-up of 11-8 years, the use of estrogen for a median of 5-9 years was associated with lower incidence of invasive breast cancer (151 cases, 0-27% per year) compared with placebo."

- **Chang, K.J. et al. (1995). Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. *Fertility and Sterility, 63,* 785-791.**

"Adding progesterone to E2 significantly reduced the proliferative effect of E2 alone. The present data shows that in vivo, 10 to 13 days of P exposure decreases the growth fraction of normal epithelial cells in the breast of premenopausal women."

"It also suggests that P or related drugs may have a therapeutic value to prevent breast epithelial hyperplasia when used > 10 days per month at approximate substitutive doses."

- **Chlebowski, R.T. et al. (2013). Estrogen plus progestin and breast cancer incidence and mortality in the Women's Health Initiative Observational Study. *Journal of the National Cancer Institute, 105,* 526–535.**

"In the Women's Health Initiative (WHI) randomised trial, estrogen plus progestin increased both breast cancer incidence and mortality. In contrast, most observational studies associated estrogen plus progestin with favorable prognosis breast cancers. To address differences, a cohort of WHI observational study participants with characteristics similar to the WHI clinical trial was studied."

"Consistent with WHI randomised trial findings, estrogen plus progestin use is associated with increased breast cancer incidence. Because prognosis after diagnosis on combined hormone therapy is similar to that of n onuser, increased breast cancer mortality can be expected".

- **Dew, J.E. et al. (2003). A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer. *Climacteric, 6,* 45-52.**

"A number of other small cohort and case-control studies have used HRT in women previously treated for breast cancer without adverse effect. None of these studies has shown an increased risk of recurrence."

"Low dose vaginal estrogens used (in this study) were estriol creams and pessaries in 36 (52%) and estradiol 25 mcg tablets in 33 (48%)."

"There was no evidence from this study to indicate any difference in the risk of recurrence of breast cancer for women using topical vaginal estrogen therapy compared with those who use no hormonal therapy."

"Limited systemic absorption has been reported with the use of vaginal estriol cream or suppositories, while marked systemic absorption can occur with Premarin cream. Endometrial proliferation has not been reported with vaginal estriol preparations."

- **Ellis, M.J. et al. (2009). Lower-dose vs. high-dose oral estradiol therapy of hormone receptor-positive, aromatase inhibitor-resistant advanced breast cancer: A phase 2 randomised study. *JAMA, 302,* 774-780.**

"Women with advanced breast cancer and acquired resistance to aromatase inhibitors were given either 6mg or 30mg daily of Estradiol. Patients showed an improvement in their disease when given Estradiol, but the 6 mg dose was better tolerated and had less side effects.

"In conclusion, 6 mg of estradiol daily, which produces estradiol levels similar to those in ovulating premenopausal women, is an active low-cost treatment for postmenopausal women with advanced breast cancer and acquired resistance to aromatase inhibitor treatment and should be further investigated."

- **Fournier, A. et al. (2005). Breast Cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *International Journal of Cancer, 114*, 448-454.**

"The association between HRT use and breast cancer risk most likely varies according to the type of progestogen used. There was no or little increase in risk with estrogens used alone or combined with micronized progesterone."

"Our study confirms previous findings of an increase in invasive breast cancer risk with estrogens combined with synthetic progestins compared to no HRT use."

"Combinations containing micronized progesterone appeared to be associated with a significantly lower breast cancer risk than those containing synthetic progestins."

- **Labrie, F. (2007). Drug Insight: Breast cancer prevention and tissue-targeted hormone replacement therapy. *Nature Clinical Practice: Endocrinology & Metabolism, 3,* 584-593.**

"Women with elevated androgen levels, whether endogenous or exogenous, experience breast atrophy consistent with the notion that androgens, *per se*, are antiproliferative for the breast."

"Androgens and DHEA, acting through the androgen receptor, have been shown in the vast majority of studies to inhibit estrogen-stimulated proliferation of human breast cancer cell lines."

"DHEA stimulates bone formation through its androgenic or anabolic component (an effect not achieved with SERMs, bisphosphonates, estrogens or calcitonin, which only decrease the rate of bone resorption)."

- **Labrie, F. et al. (2009). Effect of one-week treatment with vaginal estrogen preparations on serum estrogen levels in postmenopausal women. *Menopause, 16.***

"Vagifem, an estradiol tablet, when administered at the 25-mcg dose, led to serum E2 levels of 80pmol/ L with values still elevated but less than 50 pmol/L at 14 hours and later."

"It des not appear reasonable or acceptable to increase serum E2 levels during breast cancer therapy when the objective of treatment with aromatase inhibitors is precisely to achieve maximal inhibition of E2 biosynthesis."

- **Tamimi, R. M. et al. (2006). Combined estrogen and testosterone use and risk of breast cancer in postmenopausal women. *Archives of Internal Medicine, 166*, 1483-1489.**

"This was a prospective cohort study in the Nurses' Health Study from 1978 to 2002 to assess the risk of breast cancer associated with different types of postmenopausal hormone formulations containing testosterone. The data was for estrogen only, testosterone only, and estrogen and testosterone therapies only."

"This study . . . specifically addressed the effect of *oral E&T* therapy as currently used in US postmenopausal women on the risk of breast cancer."

"Epidemiologic studies demonstrate that circulating levels of testosterone are associated with an increased risk of breast cancer among postmenopausal women, independent of circulating estrogen levels."

"The majority of in vitro studies using breast cancer cell lines report that androgens have inhibitory effects on the proliferative effects of estrogen"

"These results are also consistent with studies showing that E&P therapies with synthetic testosterone-derived progestogens are associated with a greater risk of breast cancer compared with those with micronized progesterone."

- **Wang, Y. et al. (2013). Androgen receptor-induced tumor suppressor, KLLN, inhibits breast cancer growth and transcriptionally activated p53/p73-mediated apoptosis in breast carcinomas. *Human Molecular Genetics,* ddt077**

"The ovarian production of androgens declines after menopause, at which time over two-thirds of female breast cancers are diagnosed, suggesting that the loss of androgens may play a role in breast cancer development."

Progesterone Therapy

- **Burry, K.A. et al. (1999). Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen. *American Journal of Obstetrics and Gynecology*, *180*, 1504-1511.**

Study looked at transdermal estradiol patch 0.5mg twice weekly and OTC progesterone cream 30mg q day for 2 wks. (started 2 days after the estradiol patch was applied) and then BID for 2 weeks.

"Even studies with low serum concentrations of progesterone have shown beneficial effects on the endometrium, suggesting a direct transit to the uterus for a "first uterine pass effect."

"Fanchin reported that 45 to 90mg vaginal progesterone gel induced normal secrectory transformation of the endometrium corresponding with plasma progesterone levels of 3.4 to 3.6 ng/ml."

"Thus it seems possible that the absorption of progesterone across mucus membranes, vaginal mucosa, and the skin may result in an increased bioavailable level of the hormone, therefore providing an endometrial effect with lower serum levels of progesterone."

"This study has demonstrated that progesterone is absorbed through the skin and that luteal levels of serum progesterone can be achieved."

- **Campagnoli, C. et al. (2005). Progestins and progesterone in hormone replacement therapy and the risk of breast cancer. *Journal of Steroid Biochemistry & Molecular Biology*, *96,* 95-108.**

"The incidence of BC (breast cancer) is two-to-three times greater in women with serum levels of estradiol or testosterone in the higher quartiles or quintiles of the distribution."

"In this study, oral micronized progesterone, contrarily to synthetic progestins, did not increase BC risk in women treated with transdermal estradiol."

"A key metabolic alteration that increases BC risk is the resistance to insulin action on carbohydrates (insulin resistance: reduced insulin sensitivity), due to genetic and nutritional factors, with consequent hyperinsulinemia."

"High levels of free testosterone have been identified as a risk factor for BC both before and after menopause."
"Estrogens, particularly orally administered estrogens, are able to counteract metabolic factors that increase the risk of BC. One way they do this is by increasing insulin sensitivity and hence lowering circulating insulin levels."

"We therefore suggest that when HRT is indicated, preparations containing progesterone and not a synthetic progestin should be used, according to a sequential or cyclic-combined regimen. In this way the risk of endometrial cancer is minimised without increasing the risk of BC"

- **Elshafie M. A. A. , & Ewies, A. A. A. (2007). Transdermal natural progesterone cream for postmenopausal women: Inconsistent data and complex pharmacokinetics. *Journal of Obstetrics and Gynaecology,* 27, 655-659.**

"Progesterone receptors were detected in the whole skin, keratinocytes and fibroblasts."

"Recommended dose range is 10-40mg daily (Drug and Therapeutics Bulletin 2001)."

"Greater than 90% of oral progesterone was found to be inactivated by enzymatic degradation in the gut and liver, resulting in low serum concentrations of the active steroid"

"The chemical structure of progesterone makes it rather hydrophobic, and the carrying capacity of plasma would, therefore, become low when it is not bound to the circulating proteins."

"It is hypothesised that transdermally delivered progesterone is a substrate for peripheral 5 alpha-reductase, and conversion to 5 alpha-reduced progestin may be a significant factor accounting to low systemic progesterone levels and pregnanediol-3-glucuronide excretion."

"Progesterone cream has a similar effect on the endometrium as the standard oral progestogen"

- **Fournier, A. et al. (2008). Unequal risks for breast cancer associated with different hormone replacement therapies: Results from the E3N cohort study. *Breast Cancer Research Treatment*, 107, 103-111.**

"E3N is a prospective cohort initiated in 1990... [With women] aged between 40 and 65 years."

"80,377 postmenopausal women.. were followed for an average of 8.1 postmenopausal years."

"Conjugated equine estrogens were only marginally used by women in our cohort (1.3%)"

"Compared with HRT never-use, use of estrogen alone was associated with a significant 1.29 fold increased risk. The relative risk was 1.00 for estrogen-progesterone, 1.16 for estrogen-dydrogesterone, and 1.69 for estrogen combined with other progestagens."

"We also observed a significantly increased risk of breast with the use of estrogen alone."

"When combined with an estrogen, progesterone may have a safer risk profile in the breast compared with some other progestagens."

"Our finding of a 1/3 fold increased breast cancer risk associated with the use of estrogen alone (almost exclusively estradiol compounds, and mostly administered through the skin) differs with that of the WHI estrogen-alone trial which found a decreased risk when oral conjugated equine estrogens were used in a population of older and often overweight women."

- **Gambrell, R. (2003). Editorial: Progesterone skin cream and measurements of absorption. *Menopause*, 10, 1-3.**

" [John] Lee maintains that saliva is the only way to measure bioavailable progesterone for dosing purposes. He stated that serum and plasma are watery and contain water-soluble (hydrophilic) substances such as water-soluble vitamins, carbohydrates and proteins. Serum and plasma do not contain fat soluble (lipophilic) substances. Sex hormones such as progesterone, estrogen, and testosterone are fat soluble steroids similar to cholesterol."

"According to Lee, only a small fraction of progesterone is carried by the watery serum, so this is not a good way to measure transdermal progesterone absorption. Lee states that the goal of progesterone supplementation is to restore normal physiologic levels that are bioavailable, which is about o.3 to o.5mg/ml in saliva. In Lee's experience, the topical dose required to achieve a saliva level of progesterone of 0.5ng/ml transdermally is 12 o 15mg per day."

- **Holtorf, K. (2009). The bioidentical hormone debate: Are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? *Postgraduate Medicine*, *121,* 1-13.**

"Four studies of patients using HRT, including either progesterone or MPA, compared efficacy, patient satisfaction, and quality of life. Women in all 4 studies reported greater satisfaction, fewer side effects, and improved quality of life when they were switched from synthetic progestins to progesterone replacement."

"Synthetic progestins have potential anti-apoptotic effects and may significantly increase estrogen-stimulated breast cell mitotic activity and proliferation. In contrast, progesterone inhibits estrogen-stimulated breast epithelial cells. Progesterone also downregulates estrogen receptor-1 in the breast, induces breast cancer cell apoptosis, diminishes breast cell mitotic activity, and arrests human breast cancer cells in the G1 phase by upregulating cyclin-dependent kinase inhibitors and downregulating cyclin D1."

"Synthetic progestins may also increase the conversion of weaker endogenous estrogens into more potent estrogens, potentially contributing to their carcinogenic effects, which are not apparent with progesterone."

"Use of unopposed postmenopausal estrogen from ages 50-60 years increased the risk for breast cancer to age 70 by 23 %."

"In contrast to the demonstrated increased risk for breast cancer with synthetic progestins, studies have consistently shown a decreased risk for breast cancer with progesterone."

"Melamend et al demonstrated that, when administered with estradiol, estriol may have a unique ability to protect breast tissue from excessive estrogen-mediated stimulation. Acting alone, estriol is a weak estrogen, but when given with estradiol, it functions as an antiestrogen."

"Synthetic progestins, in contrast (to progesterone), have completely opposite effect: they promote atherosclerotic plaque formation and prevent the plaque-inhibiting and lipid- lowering actions of estrogen."

"Transdermal estradiol, when given with or without oral progesterone, has no detrimental effects on coagulation and no observed increased risk for venous thromboembolism"

"Synthetic progestin can significantly increase insulin resistance, when compared with estrogen and progesterone."

- **Leonetti, H.B. et al. (2003). Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium. *Fertility and Sterility, 79*.**

This was a blinded study were participants were given daily 0.625mg of CEE and twice daily transdermal progesterone cream either 0%, 1.5 % or 4.0% for 28 days. An endometrial biopsy was performed after treatment. No increased risk of hyperplasia was found, and it was concluded that progesterone cream has an antiproliferative effect on the endometrium.

- **Skouby, S.O. & Jespersen, J. (2009). Progestins in HRT: Sufferance or desire? *Maturitas, 62,* 371-375.**

"There is mounting evidence that natural progesterone improves cardiovascular function in contrast to the synthetic progestin medroxyprogesterone acetate (MPA) used in the large scaled US investigations."

"Progesterone is rapidly cleared from the blood, which can present challenges regarding serum progesterone testing."

"Orally administered progesterone, even in micronized form, shows a wide variation of absorption and bioavailability in the individual person."

Relative binding affinities of progesterone and synthetic progestins to steroid receptors:

	PGR	AR	ER	GR	MR
Progesterone	50	0	0	10	100
Chlormadinone acetate	67	5	0	8	0
Cypoterone acetate	90	6	0	6	8
MPA	115	5	0	29	160
Megestrol acetate	65	5	0	30	0
Nomegestrol	125	6	0	6	0
Drospirenone	35	65	0	6	230
Norethisterone	75	15	0	0	0
Levonorgestrel	150	45	0	1	75
Norgestimate	15	0	0	1	0
Desogestrel	150	20	0	14	0

PGR: progesterone, AR: androgen, ER: Estrogen, GR: glucocorticoid, MR: mineralocorticoid

"Estrogens in replacement dosages improve insulin secretion, insulin sensitivity and elimination rate in normal and hyperinsulinaemic postmenopausal women, while added progestins may reverse part of this improvement (levonogestrel > MPA > norethisterone)."

"HRT improved glycemic control in postmenopausal women with type 2 diabetes and accordingly may improve some aspects of the menopausal metabolic syndrome."

"The combination of non-oral administration of estradiol and local delivery of a progestin such as levonogestrel by means of gels, sprays, vaginal rings or intrauterine systems represent new methods of replacement therapy for the menopausal woman, improving compliance and minimizing the risks"

- **Vashisht, A. et al. (2005). A study to look at hormonal absorption of progesterone cream used in conjunction with transdermal estrogen. *Gynecological Endocrinology,* 21, 101-105.**

"Menopausal women were given 1mg estradiol gel and 40mg progesterone cream daily."

"There were significant reductions in anxiety, depression, vasomotor symptoms and libido problems compared with baseline ($p < 0.001$)."

"By use of 30-60mg of progesterone cream, luteal levels could be achieved."

"We also found the incidence of side effects to be low."

- **Wardhana, S. E.E. et al. (2013). Transdermal bio-identical progesterone cream as hormonal treatment for osteoarthritis. *Acta Med Indones*, *45*(3), 224-32.**

"The bio-identical progesterone shows its anti-inflammatory effects in OA by suppressing gene expressions in the production of inflammatory cytokines through the negative interaction between nuclear transcription factor and the progesterone receptor and/or the progesterone–induced increase of nuclear transcription factor inhibition in the nucleus. The bio-identical progesterone may indirectly regulate bone remodeling and may also play a role in the development and maintenance of cartilage. This review will discuss about transdermal bio-identical progesterone cream as suggested hormonal treatment of OA, based on its pathogenic process."

Estrogen Therapy

- **Boothby, L.A. et al. (2004). Bioidentical hormone therapy: A review. *Menopause*, *11*, 356-367.**

"Estrogen receptor alpha is mostly found I the endometrium, breast-cancer cell, and ovarian stroma cells, whereas estrogen receptor beta is mostly found in the kidney, intestinal mucosa, lung parenchyma, bone marrow, bone, brain, endothelial cells, and the prostate gland."

Binding affinities for estrogen receptor alpha and beta:

	Estrogen receptor Alpha	Estrogen receptor Beta
17-beta-estradiol	100	100
17-alpha-estradiol	58	11
Estriol	14	21
Estrone	60	37
4-OH-estradiol	13	7
2-OH-estrone	2	0.2
Tamoxifen	4	3
Raloxifene	69	16
Genistein	4	87
Coumestrol	20	140

"According to John Lee, MD. Normal salivary progesterone concentrations. . . can usually be obtained with topical doses of 15 mg per day."

- **Collaborative Group on Epidemiological Studies of Ovarian Cancer. (2015). Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. *The Lancet* 385, 1835-1842.**

"Ecological studies have shown correlations between dramatic reductions in use of HRT in many countries, and declines in the rates of breast cancer in older women."

"Meta-analyses of data from the trials and observational studies show that the increase in breast cancer risk is greater for combined estrogen–progestin therapies compared with estrogen alone."

- **Laliberte, F. et al. (2011). 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, 18,* 1052-1059.**

"After adjustment for confounding factors, ETS (transdermal) was associated with a statistically significant risk reduction for VTE and hospitalization-related VTE by 33% and 62%, respectively, compared with the oral estrogen-only HT cohort. Of note, the risk reduction associated with ETS was more pronounced for PE events."

"[These findings] are consistent with results from ESTHER, Renoux et al, and Cononico et al."

- **Maki, P. et al. (2010). Summary of the National Institute on Aging-sponsored conference on depressive symptoms and cognitive complaints in the menopausal transition. *Menopause,* 17, 815-822.**

"Clinical trial evidence indicates that estradiol therapy can be effective in treating perimenpausal depression."

"Estrogen alters monoaminergic systems (e.g.: serotonin and noradrenalin) that are intimately involved in mood and behavior regulation. For example, estrogen increases serotonin receptor density in select brain regions such as the hypothalamus, preoptic area, and amygdala. Estrogen also increases noradrenalin availability and synthesis, while reducing its turnover."

"When depression is present, CHD prognosis is poor."

"In a secondary analysis, women who initiated HT before the final menstrual period had higher memory scores compared with women who initiated HT after menopause."
"Estradiol has significant positive effects on brain cholinergic neurons, interacts with trophic factors on neuronal development and plasticity, and improves cholinergic-related cognitive processes in animal models."

- **Mueck, A. O. (2012). Postmenopausal hormone replacement therapy and cardiovascular disease: the value of transdermal estradiol and micronized progesterone. *Climacteric*, *15*(sup1), 11-17**

"There is a wealth of evidence to suggest that, unlike oral estrogens, transdermal estradiol does not increase the risk of venous thromboembolism, probably due to its lack of effect on the coagulation cascade, including thrombin generation and resistance to activated protein C, and does not increase the risk of stroke. It is cardioprotective, signifi cantly reducing the incidence of myocardial infarction compared with non-users; it signifi cantly reduces the incidence of new-onset diabetes, a risk factor for myocardial infarction."

"Micronized progesterone has also been shown not to increase the risk of venous thromboembolism and further reduced the incidence of new-onset diabetes when combined with transdermal estrogen. Micronized progesterone has a neutral effect on the vasculature, including a neutral or beneficial effect on blood pressure. Therefore, experimental and clinical data indicate that transdermal estradiol and micronized progesterone could represent the optimal HRT, particularly in women at risk of adverse events."

Thyroid

- A**ksoy, D.Y. et al. (2005). Effects of prophylactic thyroid hormone replacement in Euthyroid Hashimoto's Thyroiditis. *Endocrine Journal, 52,* 337-343.**

"Early treatment of euthyroid Hashimoto's thyroiditis patients with L-thyroxine may slow down not only the disease process itself but through its immune modulating events it may also affect the course of other auto-immune diseases which accompany."

- **Ma, S. G., et al. (2014). A novel treatment for subacute thyroiditis: administration of a mixture of lidocaine and dexamethasone using an insulin pen. *Mayo Clinic Proceedings*, 89, No. 6, 861-862.**

"Patients with subacute thyroiditis (SAT) generally have neck pain and fever. No fast-acting therapy has been reported. We hypothesised that intrathyroidal injection using an insulin pen filled with a mixture of lidocaine and dexamethasone could produce therapeutic benefit compared with oral medications"

"Insulin cartridges were filled with 3.0-mL mixtures that contained 50 mg of lidocaine, 3 mg of dexamethasone, and saline solution. The thyroid isthmus was injected with a 4-mm needle (32G) and the lobe with a 6-mm needle (32G) under ultrasound guidance."

"Most patients in the injection group reported rapid pain relief and significant neck relaxation within 1 week compared with the oral group (**P**<.0001). In addition, the frequency and duration of treatments were significantly less (**P**<.0001)."

- **Yamada, T. et al. (1978). An increase of plasma triiodothyronine and thyroxine after administration of dexamethasone to hypothyroid patients with Hashimoto's Thyroiditis. *Journal of Clinical Endocrinology and Metabolism,* 46, 784-790.**

Plasma T4 and T3 increased in all patients after administration of 2 mg dexamethasone for 4 weeks. The increase was greater in T3 than in T4.

Dexamethasone inhibits the peripheral conversion of T4 to T3, and also decreases TSH.

Androgen Therapy – Testosterone

- **Bachman, G. et al. (2002). Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. *Fertility and Sterility,* 77, 660-665.**

"Androgens affect sexual desire, bone density, muscle mass and strength, adipose tissue distribution, mood, energy, and psychological well-being."

"Recognised causes (of Androgen Insufficiency) include hypopituitarism, Addison's disease, corticosteroid therapy, ovarian failure or oophorectomy, and oral estrogen replacement therapy or oral contraceptive use."

"Symptoms of androgen insufficiency most often reported in the literature include (1) a diminished sense of well-being or dysphoric mood; (2) persistent, unexplained fatigue; and (3) sexual function changes, including decreased libido, sexual receptivity, and pleasure."

"A diagnosis of androgen insufficiency should only be made in women who are adequately estrogenised."

"Free T values should be at or below the lowest quartile of the normal range for the reproductive age (20-40 years), in conjunction with the presence of clinical symptoms and adequate estrogen status."

- **Basaria, S., et al. Clinical review: Controversies regarding transdermal androgen therapy in postmenopausal women. *The Journal of Clinical Endocrinology & Metabolism,* 91, 4743-4752**.

"The climacteric ovary contributes 50% of testosterone and 30% of androstenedione to the circulation."

"Oophorectomised women may be the ideal candidates for androgen replacement."

The clinical symptoms of androgen deficiency include diminished well-being or dysphoric mood, persistent unexplained fatigue, and sexual dysfunction (decreased libido, responsivity or pleasure).

"These modalities resulted in supraphysiological and unpredictable levels of testosterone (injections and pellets), whereas oral preparations resulted in an adverse lipid profile and were potentially hepatotoxic (methyltestosterone)."

- **Dimitrakakis, C., et al. (2003). A physiologic role for testosterone in limiting estrogenic stimulation of the breast. *Menopause,* 10, 292-298.**

"The present study provides multiple lines of evidence suggesting that this estrogen exposure risk for breast cancer may be attenuated by androgens."

"The demonstration in the present study that administration of an AR (androgen receptor) antagonist enhances mammary epithelial proliferation in normal female monkeys confirms that endogenous androgens normally inhibit this proliferation."

"A major androgenic effect demonstrated in this in vivo study is the down-regulation of ER alpha and up-regulation of ER Beta expression, resulting in reversal of the ER alpha-dominant receptor ratio found in E2 treated mammary epithelium."

"Interestingly, a reciprocal or inverse relationship between expressions of these two ERs is also reported I breast cancer tissues, where ER B expression is also inversely correlated with proliferation"

- **Mazer, N. et al. (2003). Transdermal testosterone for women: A new physiological approach for androgen therapy. *Obstetrical and Gynecological Survey,* 58, 489-500.**

Healthy women produce about 300mcg per day of testosterone.

"The 5 alpha reductase and aromatase activities present in the epidermal layer of nongenital skin (such as the abdomen) are relatively small, the degree of first-pass dermal metabolism of testosterone to dihydrotestosterone (DHT) and estradiol (E2) is likewise expected to be small when using a non-genital transdermal patch"

Giving testosterone orally can cause "marked reductions in the concentrations of SHBG and thyroxine-binding globulin, which may impact hormone bioavailability, and HDL cholesterol, which may adversely affect cardiovascular risk.

"The individual patient who requires both testosterone and ET, the use of transdermal E2 would result in a substantially greater increase in free testosterone levels than if oral estrogen therapy were given concomitantly with a testosterone matrix patch"

- **Miller, B. et al. (2000). Sublingual administration of micronized estradiol and progesterone, with and without micronized testosterone: effect on biochemical markers of bone metabolism and bone mineral density. *Menopause,* 7. 318-326.**

"The addition of androgens to HRT has been shown not only to improve sexual health but also to prevent bone loss. In fact, androgen receptors have been found in bone cells of both men and women. Whereas estrogen decreases bone resorption, androgens may promote bone deposition by increasing osteoblastic activity."

"The addition of methyl-testosterone to HRT in postmenopausal women has been reported to adversely affect lipid profiles, and may have hepatotoxic effects."

"The sublingual administration of micronized testosterone also avoids first passage through the liver, which may preclude the unfavorable lipoprotein effects.'

The study used either micronized estradiol 0.5mg or micronized estradiol 0.5mg plus micronized testosterone 1.25mg, and micronized progesterone 100mg if they had a uterus. This regimen was given BID.

"Micronized E2, P4, and T therapy increased BMD of both the lumbar spine and hip, whereas micronized D2 and P4 increased spinal BMD and maintained hip BMD."

"It has been suggested that progestogens may stimulate bone formation independent of estrogen. Although the synthetic nortestosterone-derived C19 progestins (i.e., noresthisterone) have been reported to have beneficial effects on bone density possibly because of their androgenic properties, the C21 progestins, MPA or P4 itself, have not consistently been shown to enhance bone metabolism."

"The results of this study indicate that besides relieving menopausal symptoms and restoring g therapeutic sex hormone levels, sublingually administered micronized E2, P4, and T successfully reduces metabolic bone markers of both resorption and formation, prevents bone loss, and results in significant increases in spine and hip BMD."

- **Slater, C. et al. (2001). Pharmacokinetics of testosterone after percutaneous gel or buccal administration" in *Fertility and Sterility*. Vol. 76, No. 1, July 2001.**

"Estrogen replacement after menopause, particularly after surgical menopause, is probably not an adequate total hormonal replacement."

"Maximum testosterone levels obtained on day 1 with the lozenge (testosterone 1 mg), . . . occurred 1 hour after administration, reaching the upper range of normal male levels. "

"With regard to the testosterone gel, maximum testosterone levels on day 1 of treatment . . . occurred at 4-18 hours after administration."

"These data suggest that testosterone gel is the preferable route of administration of testosterone because the gel provides prolonged levels of total testosterone. The commonly prescribed doses of 1 mg of micronized testosterone gel. . appear(s) to be excessive."

Androgen Therapy – DHEA

- **Labrie, F. (2010). DHEA after menopause: Sole source of sex steroids and potential sex steroid deficiency treatment. *Menopause Management*, 19, 14-24.**

"Postmenopausal women suffering from vaginal atrophy received daily DHEA or placebo intravaginally for 3 months. A rapid and very marked improvement of all the symptoms and signs of vaginal atrophy was observed, with no change in circulating estradiol or testosterone."

"Other clinical data suggests that DHEA could also exert beneficial effects on bone and muscle loss, skin atrophy, adiposity and type 2 diabetes."

"This marked reduction in the secretion of DHEA by the adrenals during aging results in a parallel fall in the formation of androgens and estrogens in peripheral target tissues, a situation believed to be associated with a series of medical problems of menopause: insulin resistance, fat accumulation, bone loss, muscle loss, type 2 diabetes, vaginal atrophy and skin atrophy, memory and cognition loss, and possibly Alzheimer's disease."

"These actions also indicate a unique activity of DHEA on bone (namely, a stimulation of bone formation) while ET, HT, bisphosphonates, selective estrogen-receptor modulators and calcitonin only reduce the rate of bone loss."
"Compared to placebo, DHEA produced a 68% improvement in the ASF arousal/sensation domain, a 39% improvement in the arousal/ lubrication domain, a 75% improvement in orgasm, and a 57% improvement in dryness during intercourse."

"There is no reason to believe that the metabolism, action and safety of exogenous DHEA given at physiologic doses to symptomatic women would be different from the metabolism and action of endogenous DHEA in women who have sufficient levels of DHEA to remain free from the symptoms of menopause."

"This is well supported by the absence of DHEA-related safety issues in the medical literature, in which high doses of DHEA have been used orally or percutaneously in a large series of women for up to 2 years."

- **Labrie, F. et al. (2007). Metabolism of DHEA in postmenopausal women following percutaneous administration. *The Journal of Steroid Biochemistry & Molecular Biology*. 103, 178-188.**

"Following cessation of estrogen secretion by the ovaries in postmenopausal women, all estrogens and almost all androgens are made locally from DHEA in the peripheral target tissues with minimal diffusion of the active steroids outside these tissues."

Subjects were given 3ml twice daily of one of the 5 concentrations: Placebo, 0.1% DHEA, 0.3% DHEA, 1% DHEA, and 2% DHEA for 13 weeks.

"It is quite clear from the present data that DHEA is preferentially transformed into androgens rather than into estrogens in postmenopausal women."

- **Labrie, F. et al. (1997). Effect of 12-month Dehydroepiandrosterone Replacement Therapy on Bone, Vagina, and Endometrium in Postmenopausal Women. *The Journal of Clinical Endocrinology & Metabolism,* 82, 3498-3505.**

Fourteen healthy 60-70 year old postmenopausal women received 10% DHEA cream in the morning, using 3-5 gm of cream daily.

"Total hip BMD increased significantly."

"The endometrial atrophy seen in all women at the start of treatment remained unaffected by 12 months of DHEA administration."

"The estrogenic stimulation of vaginal cytology in the absence of any sign of stimulatory effect on the endometrium is of potentially major interest for the prevention and management of menopause."

"Our data also confirm the beneficial effects of DHEA on well-being and energy reported previously."

"Our data show that DHEA, a compound with a predominantly androgenic influence, has apparently no deleterious effect on the serum lipid profile."

- **Labrie, F. et al. (2008). Effect of intravaginal DHEA on serum DHEA and eleven of its metabolites in postmenopausal women. *Journal of Steroid Biochemistry and Molecular Biology,* 111, 178-194.**

This study used 10 subject per arm to receive placebo, 6.5mg DHEA, 13mg DHEA, or 23.4 mg DHEA daily.

"The present data show for the first time that the intra-vaginal administration of DHEA can rapidly increase the maturation index and decrease the pH in vaginal atrophy. Most importantly, this effect is achieved while maintaining serum estrogen levels within the values found in normal postmenopausal women, this avoiding the risk of breast or uterine cancer."

"It is of major interest that endometrial biopsies performed at the end of the 12-month therapy with a high daily DHEA dose (4g of a 10% DHEA cream applied on the skin) showed atrophy in all women, thus indicating that the human endometrium does not possess the enzymes required to transform DHEA into estrogens and eliminates the need for the addition of a progestin to avoid the risk of uterine cancer."

- **Labrie, F. et al. (2009). Intravaginal dehydroepiandrosterone (Prasterone), a physiological and highly efficient treatment of vaginal atrophy. *Menopause,* 16, 907-922.**

This was a phase III, multicenter, randomised, placebo-controlled, and double-blind trial planned for 50 participants per arm. Women were given either placebo, 0.25% DHEA (3.25mg), 0.5% DHEA (6.5mg), or 1% DHEA (13mg) applied intravaginally at bedtime.
"Our recent preclinical data have shown an important effect of DHEA on all three layers of the vaginal wall, including the collagen fibers of the lamina propria and the muscularis."

"Although DHEA can be transformed into both androgens and estrogens in the mammary gland, the global effect of DHEA on the human mammary gland is inhibitory."

"Because the only variable source of sex steroids available in postmenopausal women in DHEA secreted by the adrenals and locally transformed in specific cells and tissues into estrogens and/ or androgens by the mechanisms of intracrinology, replacement with DHEA seems to be the only physiological replacement therapy for postmenopausal women experiencing menopausal symptoms."

- **Labrie, F. et al. (2009). Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in postmenopausal women. *Menopause,* 16, 923-931.**

This was more data from the above study looking specifically at sexual function.

"The present data show . . . that local intravaginal treatment with DHEA. . . causes a marked improvement for all four aspects of women's sexual dysfunction, namely, desire/ interest, arousal, orgasm, and pain at sexual activity."

"In postmenopausal women with normal adrenal function, and increase in sexual excitation and libido was reported at 6 months of DHEA administration."

- **Labrie, F. DHEA, important source of sex steroids in men and even more in women. Chapter 4. In *Progress in Brain Research,* 182, 97-148.**

"No serious adverse event related to DHEA has ever been reported in the world literature (thousands of subjects exposed) or in the monitoring of adverse events by the FDA (millions of subjects exposed) thus indicating, as expected from its known physiology, the excellent safety profile of DHEA."

The author listed 50 separate studies using DHEA doses from 25mg up to 700mg orally and did not report any negative effects.

"The androgens testosterone and DHT as well as E2 made in peripheral tissues from DHEA of adrenal origin exert their action locally in the same cells where their synthesis takes place. This sophisticated mechanism permits to maintain biologically active levels of intracellular estrogens and/ or androgens in specific tissues in need of these sex steroids while the same steroids leak in the blood at very low levels, thus sparing the other tissues from a potentially negative influence."

"When DHEA was Analysed from 17 different (OTC) formulations, 3 formulations contained no detectable DHEA while most tablets/ capsules had 59-82% of the amount indicated on the label while one tablet had 149% of the amount of DHEA stated."

"In the human, data indicate that DHEA inhibits atherosclerosis, reduces cardiovascular risk markers, and improves endothelial function."

"It has been found that women who underwent bilateral oophorectomy before age 45 experienced an increased mortality associated with CVD compared with referent women."

- **Slayden, S. M. et al. (1998). The Effect of 17B-Estradiol on adrenocortical sensitivity, responsiveness, and steroidogenesis in postmenopausal women. *Journal of Clinical Endocrinology and Metabolism, 83*, 519- 524.**

"Adrenopause may in part be responsible for the increasing incidence of cardiovascular disease, glucose intolerance, cancer, and the decline in bone mass and immune competence with age."

"It is unlikely that the hypoestrogenism of menopause contributes to the decline in AAs noted with age. Furthermore, menopausal estrogen replacement, at least in physiological amounts administered transdermally, cannot be expected to reverse the suppressed production of these androgens."

Cortisol

- **Beral, V. et al. (2011). Breast cancer risk in relation to the interval between menopause and starting hormone therapy. *Journal Natl Cancer Inst,* 103, 296-305.**

"The greatest excess risk (of breast cancer) was among current users of estrogen-progestin hormonal therapy, but risk was also statistically significantly increased in users of estrogen- only preparations and of tibolone (a synthetic steroid with estrogenic, progestogenic, and androgenic activities that is licensed in Europe but not in the United States)"

"Some of these findings confirm what is already well known, for example, that current users of estrogen-progestin preparations are at the greatest risk of breast cancer and that the associated risk increases with duration of use."

"We found greater risks of breast cancer if hormonal therapy use began either before or soon after menopause than after a longer gap; and this pattern of risk was seen across different types of hormonal therapy"

- **Cagnacci A. et al. (1997). "Melatonin enhances cortisol levels in aged women: Reversible by estrogens" in J of Pineal Research 1997; 22L 81-85.**

"In a previous study, we had shown that in PMW the administration of a huge dose of melatonin (100mg) is capable of unmasking the critical regulation of HPA axis and markedly enhancing cortisol levels. The present study shows that this stimulatory effect of melatonin on cortisol is nullified by estrogen supplementation."

"The possibility that estrogens improve the control of the HPA axis and reduce the increase of cortisol after stimulation and/or at selected circadian times, may prove important for the prevention of metabolic and cardiovascular alterations of postmenopausal women."

- **Cagnacci, A. et al. (2011) Increased cortisol level: a possible link between climacteric symptoms and cardiovascular risk factors. Menopause, 18, 273-278.**

"Several pieces of evidence indicate that depression and anxiety, whose scores increase in the perimenopause and early postmenopause, can be associated with elevated adrenocortical activity."

- **Edwards, L. et al. (2011). Hypocortisolism: An evidence-based review. Integrative Medicine, 10, 26-33.**

"Many clinical syndromes, including "burn out, " fibromyalgia (FMS), posttraumatic stress disorder (PTSD), autoimmunity, allergies, inflammation, and chronic pelvic pain, have been associated with HPA axis dysfunction and hypocortisolism"

"When chronically elevated, cortisol has potent metabolic effects as a catabolic hormone in all organs and tissues except the liver. Systemic effects of elevated glucocorticoids include increased gastric acid secretion, decreased collagen production, reduced diuresis, reduced bone formation, hyperglycemia, and hippocampal neuronal damage. Cortisol also impairs thyroid hormone production and function and causes numerous aberrations in immune system regulation and function."

Theories on Pathophysiological Evolution of Hypocortisolism:

1. Developmental

   "After an initial period of HPA axis hyperactivity and cortisol hyper-secretion, hypocortisolism may ultimately develop as a type of maladaptive "overcompensation" of the self-preservation mechanisms designed to protect the metabolic machinery (in particular the brain) from the effects of persistent cortisol elevation."

2. CRF Down regulation

   "An increase in the sensitivity of the HPA axis to cortisol during periods of excessive glucocorticoid production induces negative feedback control on further release of stimulating hormones, thereby resulting in hypocortisolism"

3. Inadequate Glucocorticoid Signaling

   "Decreased glucocorticoid bioavailability accounts for one possible mechanism and may develop secondary to decreased adrenal cortisol production, alterations in cortisol binding protein levels, enzymatic conversion of cortisol to other hormones, or action of the "multidrug resistant pump, " which potentiates cortisol exit from the cell."

4. Intrinsic Adrenal Gland dysfunction

   "In the face of adrenocortical atrophy, glucocorticoid production would diminish and compensatory glucocorticoid receptor up regulation does not occur.

5. Adaptive Response

   "Hypocortisolism may occur as an adaptive survival mechanism to promote a more vigorous immune response."

   "Breast Cancer patients who demonstrate significant post-treatment exhaustion have been shown to have significantly altered HPA axis activity in combination with elevated IL-6 levels and flattened cortisol curves with an apparent consequential increase in mortality and metastasis."

   "Diseases such as obesity, increased coronary artery calcification, and metabolic syndrome have been linked to circadian abnormalities in cortisol, particularly flattened cortisol curves."

- **Head, K. A. (1998). Estriol: Safety and efficacy. *Alternative Medicine Review,* 3**

"Estriol has a much lower affinity for binding to SHBG; therefore, a greater percent is available for biological activity."

"One mg intravaginal estriol resulted in serum levels equivalent to 10mg of the orally administered hormone."

"When given alone, it generally exerts an estrogenic effect, the strength of which depends on the dosage. When given in conjunction with estradiol, it appears to exert antagonistic effects"

"Estriol succinate may have less thrombotic potential than synthetic estrogens"

"Estriol appears very effective for the treatment of menopausally- related urinary incontinence, urgency, and persistent UTIs."

"Daily use of intravaginal estriol is safe and without risk of endometrial proliferation or hyperplasia."

"Due to conflicting reports on the effect of estriol on the endometrium, it is probably wise to prescribe a natural progesterone in conjunction with the estriol for a period of at least 10-14 days per month in order to shed any uterine tissue which may have built up as a result of the estriol administration."

"Estriol is probably a safer form of estrogen replacement in regard to breast cancer for the following reasons: 1) *In vitro,* when given in conjunction with estradiol, it accelerates the removal of estradiol bound to protein receptors; 2) investigators have been able to initiate very little carcinogenesis in animal studies unless large doses (200-500mcg/kg/day) were used on a continuous basis; 3) in animal studies it has been found to prevent carcinogen-induced mammary tumors; and 4) unlike estrone and estradiol, estriol metabolism does not result in the formation of large numbers of potentially carcinogenic substances."

- **Qureshi, A. C. et al. (2007). The influence of the route of estrogen administration on serum levels of cortisol-binding globulin and total cortisol. *Clinical Endocrinology*, 66, 632-635.**

"Salivary cortisol is a validated marker of free cortisol, although it is not commonly used in clinical practice"

"Oral estrogen preparations as routinely used in the clinical setting result in marked increases in total cortisol concentrations due to increased CBG levels. Transdermal estrogen preparations do not appear to alter CBG or cortisol concentrations.