

"Natural" Hormone Replacement Therapy (NHRT) What We Know & Don't Know

PHILOSOPHY OF NHRT

- ◆NHRT attempts to restore a "bio-identical" hormone balance by replacing in a way that mimics the body's natural hormonal pattern. This may include use of the three human estrogens (estrone, estradiol, & estriol), progesterone, testosterone, & DHEA.
- ◆The term "natural" is misleading as many products regarded as conventional are also derived from natural plant sources.
- ◆Publications & presentations on NHRT make claims about natural estrogen and progesterone yet rely on studies that have used Premarin[®] +/- medroxyprogesterone (MPA). Though unsubstantiated, NHRT assumes all the HRT benefits but none of the risks.¹
- ◆NHRT particularly dislikes conjugated equine estrogen.
- ◆NHRT highlights the role of estriol. Proponents claim a protective effect against breast & endometrial cancer.
- ◆NHRT promotes progesterone over synthetic progestins (e.g. MPA) to avoid common adverse effects.

ESTROGEN

- ◆**Triest cream**, made by a compounding pharmacist, contains the estrone 10%, estradiol 10%, and estriol 80% (synthetically derived from plant sources). One would expect good absorption, as seen with other natural estrogen products (e.g. estradiol patches & gels). There does not appear to be any published studies specifically on Triest cream.
- ◆**The role of estriol**: The estrone and estradiol components of triest cream have well recognized estrogenic effects, while estriol has very weak and short acting estrogenic effects. Its highly promoted benefits of protecting against breast and endometrial cancer are equivocal. The limited literature available is based on animal studies and some epidemiological data.² As a low potency agent, it is somewhat safer than other estrogens; however, continuous use in high doses may have stimulatory effects on breast and endometrial tissue.³ One case-control study found systemic (oral) but not vaginal estriol increased the risk of endometrial neoplasia and atypical hyperplasia (odds ratio 3.0 & 8.3 respectively).⁴ Evidence is conflicting regarding estriol's potential to prevent postmenopausal osteoporosis (PMO).⁵ There is no clinical evidence that it protects against breast cancer, colon cancer, or PMO.⁶
- ◆**Intravaginal estriol** may be used for local urogenital complaints and appears to be safe. The effects on the endometrium are variable, depending on the dose. One review found no increased risk of endometrial proliferation or hyperplasia.⁷ However, another study found no difference between the effects of estradiol and estriol.⁸
- ◆There are many **commercial products** containing **estradiol or estrone from natural plant sources** (e.g. C.E.S.[®], Estrace[®], Ogen[®], Estraderm[®], Vivelle[®], Oesclim[®], Climara[®], and Estroge[®]).

PROGESTERONE

- ◆Natural progesterone (Prometrium[®]) is well absorbed following oral administration but is ~90% metabolized after the hepatic first pass. This can limit the potential for once daily administration and results in high levels of progesterone metabolites which can cause dizziness and drowsiness.⁹ Taking progesterone in the evening will minimize these side effects, and is advantageous in women who have difficulty sleeping. Synthetic progestins (medroxyprogesterone, norethindrone) resist the first pass effect, but can have undesirable effects on the liver and cause more side effects. Alternate delivery methods are being studied for their potential role. Most claims for progesterone actually rely on studies using MPA.
- ◆Dr. JR Lee's book on natural progesterone makes many claims for progesterone and promotes its use even for women without a uterus;¹⁰ however, evidence is lacking. (This goes against the current accepted standard of practice.⁶)

Percutaneous Absorption Of Progesterone

- ◆One small study (n=6) looked at progesterone cream (30 & 60mg/day) and found percutaneous absorption of progesterone correlated with the absorption of transdermal 17-beta-estradiol. It concluded that the route was safe & effective.¹¹
- ◆There is **no evidence** that percutaneous progesterone creams offer protection against endometrial cancer.¹¹ Until such evidence is established, women desiring the NHRT may be treated with oral progesterone (Prometrium[®]).

Progesterone Vaginal Cream/Gel

- ◆Vaginal administration of progesterone is more highly absorbed than oral.^{12,13} A sustained release vaginal gel (Crinone 4% & 8%), now available in the U.S., has been shown to produce gestational changes and is well-tolerated.^{14,15,16,17}

ANDROGENS

- ♦ Androgens may be indicated for symptomatic women undergoing natural or surgical menopause. This area has received recent media attention including a "thumbs up" from Oprah Winfrey. Androgen therapy should be used judiciously in natural menopause as evidence is lacking for a true deficiency state.¹⁸ All androgens have virilizing effects, and some may have adverse hepatic effects. The relatively low doses given to women (as compared to men) are not likely to have adverse hepatic effects.¹⁹ Monitoring for other side effects is very important, giving evidence for the need to decrease or discontinue the dose. Caution is warranted as androgens may increase the risk of estrogen related cancers.
- ♦ Topical testosterone reduces fat, and total body weight without adverse effects on lipids.²⁰
- ♦ Vaginal testosterone may be indicated in some women for the treatment of decreased libido &/or urogenital atrophy.
- ♦ Commercially available androgens include oral testosterone undecanoate (Andriol® 40mg cap EOD) and Climacteron Inj. (a combination of testosterone enanth. and estradiol dianthate). The recommended dose of Climacteron Inj. has been reduced to 0.5ml IM Q4-6 weeks to avoid virilization and habituation.
- ♦ Studies regarding the optimal testosterone product, dose, and long term safety are lacking.

DHEA

- ♦ The adrenal androgen, dehydroepiandrosterone (DHEA), declines with age. DHEA is promoted as somewhat of an anti-aging miracle drug for mood, depression, sleep, and cardiovascular effects.
- ♦ Adverse effects include liver dysfunction, virilization, adverse lipid changes, and possible hepatocarcinogenicity.²¹
- ♦ Some preliminary studies have suggested DHEA replacement may have benefits such as enhancement of the immune system. The area is still investigational given the lack of long term study.²²

OTHER NATURAL APPROACHES TO MENOPAUSE

- ♦ General measures that have long-term benefits include:
- ♦ Calcium and Vitamin D: increasing daily intake to ~1500mg and 800-1000 I.U. respectively helps to prevent PMO.
- ♦ Food sources of phytoestrogens (e.g. soybean, linseed, tofu) have estrogen like activity with varied beneficial effects on lipids, reducing breast cancer, hot flushes, and vaginal dryness.
- ♦ *Black Cohosh* has been studied and appears to be a useful alternative for short term relief of menopausal symptoms.
- ♦ Other herbs may be considered for menopausal conditions: *St. John's Wort* (mild depression), *Ginkgo biloba* (memory impairment), valerian (sleep disturbances). Herbs for which data do not support their use include: *Ginseng*, *Dong Quai*, and *Evening Primrose Oil*.

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