HORMONE THERAPY FOR WOMEN IN EARLY MENOPAUSE : A 2008 UPDATE

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We entered the millennium with the certainty that, based on years of accumulated data from many large observational studies as well as a number of smaller RCT's postmenopausal hormone therapy was not only effective for the treatment of menopausal symptoms but provided a host of other health benefits most notably cardioprotection, reduced mortality, and protection against bone loss.

All that changed in 2002 with the WHI report that breast cancer, heart disease strokes and pulmonary emboli were all increased in women on EPT.

↑***Breast Cancer***	**26 %**
↑**CHD**	**29%**
↑**Stroke**	**41%**
↑**PE**	**113 %**

Highly significant reductions in all fractures (including hip fractures), as well as of colorectal cancer and diabetes remained unnoticed.

Few even heard the results of the E only Arm of the WHI study reported in 2004 ; fewer CHD events,and fewer cases of breast cancer both of which just missed being statistically significant overall + a highly significant reduction in all fractures, with a lesser reduction in.Diabetes Mellitus and colorectal cancer.

A 2006, comparison of 30 year data from the Nurses' Health Study (NHS) a large observational trial, with the WHI revealed remarkable homology across all areas except the CVSystem, where there was a 30-40% reduction in CVS events in the NHS study population and a 30% increase in the WHI group. *An insightful analysis clearly pointed to patients' age at enrollment as the significant difference:* in the NHS it was 30-55 years and the mean in the WHI was 63 years. That age was a factor was confirmed in a secondary analysis of the older population of the NHS and of the younger 50-59yo/ symptomatic, recently menopausal subgroup of the WHI population.

Recent (2008) summaries from both NAMS and IMS papers specifically address the prescribing of ET/EPT to women in early menopause. The NAMS position paper[1] sets forth

recommendations based on a review of new evidence by an expert committee, and has been endorsed by numerous organizations including The Endocrine Society, and the Society of Obstetricians and Gynecologists of Canada(SOGC). The IMS paper [2] is the official 2008 summary of the First IMS Global Summit on menopause-related issues and does the same.

In the absence of specific contraindications, hormone treatment with either ET or EPT, is generally accepted and recognized as the best and most effective therapy for ***vasomotor symptoms.*** Similarly, symptoms related to ***vulvar and vaginal atrophy*** (e.g. vaginal dryness, dyspareunia and atrophic vaginitis) respond best to estrogen containing products (ET or EPT) both systemic and local. When complaints are limited to vulvovaginal symptoms, local vaginal therapy is generally recommended. ET also improves ***bladder symptoms:*** Local ET decreases the incidence of *UTI's* and may also reduce symptoms of *urge incontinence* and of *overactive bladder*. The effects on *stress incontinence* remain controversial.

The ***increase in weight*** and in ***BMI*** is common in midlife, peaking between 50-59 years of age is attributable to a number of factors including increased caloric intake + decreased caloric expenditure (less exercise!), a decrease in metabolic rate, and possibly hormonal changes associated with menopause. However, evidence from clinical trials indicates that, in comparison to the placebo group, neither ET nor EPT is associated with any significantly greater weight gain or increase in BMI.

Data from both observational and RCT's shows that long term use of HT (ET/EPT) reduces ***bone loss,*** prevents the development and progression of ***osteoporosis,*** and reduces ***fractures*** at all sites (including thehip) by 35-40%, even in those low at risk for osteoporosis. Lower than standard HT doses prevent bone loss and even modestly increase BMD. ET/EPT also has positive effects on osteoarthritis and on maintenance of intervertebral discs. *Both NAMS and IMS recommend that for women with low bone mass and without specific contraindications to ET/EPT extended or long term use of ET/EPT should be considered, even in the absence of vasomotor symptoms, particularly when alternate (antiresorptive) therapies are not appropriate or are associated with unacceptable side effects. IMS recommends that, given the recognized benefits of ET/EPT, that, despite the lack of head to head clinical trials comparing ET/EPT to bisphosphonates or other antiresorptives.,in women 50-59 yo, HRT be considered a safe and cost effective first line treatment for the prevention of osteoporotic fractures.*

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With respect to the **cardiovascular** system, it is quite clear that "***Reproductive stage is a major determinant of the effect of estrogens on atherosclerosis progression, complications and***

plaque vulnerability”[3]. Evidence is increasing that ET/EPT initiated during the perimenopause/early postmenopause but not in late menopause, inhibits the progression of atherosclerosis, whereas initiation of treatment at the complicated plaque stage of atherosclerosis is associated with potentially adverse vascular effects including plaque destabilization and possible rupture resulting in an acute coronary event.

In the WHI, women who began ET at 50-59 yo and within 10 years of menopause, like observational trial participants, were at decreased **risk for CHD** compared to placebo group. For the duration of the study (up to 8 years), there was no increase in CHD risk in women who initiated (ET/EPT) before age 70. Longer duration of therapy (>5 years) appears to decrease CHD risk, although, older women and those more distant from menopause at initiation of HT may be at increased risk in the short term.
Postmenopausal HT in standard doses does not prevent or reduce the occurrence of ***strokes,*** *and thus cannot be recommended for primary or secondary stroke prevention.* However, NHS data suggest that lower doses (e.g CEE 0.3 mg) may not increase risk.

The **VTE risk** though doubled, in 50-59 yo women is still “rare” i.e. <1/1000 women per year of ET/EPT use. The risk increases within the first 1-2 years of treatment then decreases over time,. Women with a Leiden V factor mutation or with a prior history of VTE are at increased risk for VTE when treated with HT
Though ET/EPT in women 50-59yo or within 10 years of menopause appears to reduce CHD risk, *“pending additional data, HT is currently not recommended as a sole or primary indication for coronary protection in women of any age”.*

Type 2 diabetes mellitus increases with age and increasing BMI. By reducing insulin resistance and/or decreasing centripetal weight gain, postmenopausal hormone therapy reduces incident diabetes mellitus: EPT by 21%, ET by 12%.)

Invasive **colorectal cancer**, was reduced by 44% in the WHI/EPT treated women, but not with estrogen alone. However, three years after discontinuation of treatment, the significant reduction in invasive colorectal cancer in the EPT treated group did not persist.[4]

The risk of **endometrial Ca** after 3 years unopposed standard dose systemic ERT is increased 5 fold, and after 10 years, 10 fold. *In women with an intact uterus, unopposed estrogen should be avoided and concomitant progestin used.*

Postmenopausal hormone therapy is not a major factor in increasing **breast cancer risk.** Significant non-modifiable factors include aging. female sex, family history, genetic predisposition. Modifiable factors e.g. obesity/weight gain, alcohol, lack of exercise and smoking should be addressed.. In the WHI/***ET*** group***,*** in all age groups there were 6 fewer (NS) breast cancers/ /10,000 w/y of use. In the **EPT** *arm* a modest increase of 4-6 breast cancers/10,000 women/year appeared after 5 years of EPT use, but was *limited to those who had used HT prior to entry* into the study and *did not occur in the 50 – 59 yo EPT users..* Mortality rate from their disease was lower in women who were diagnosed with breast cancer while on HT.

The IMS provided an important update regarding the widely publicized US decrease in **breast cancer** between 2002-2007 which was attributed to the mass discontinuation of HT, not only in the US but also worldwide. However in spite of this, --there was no decline in breast cancer in other countries in the world, including Canada where, unlike the US, the established breast screening programs continued without change – despite the fact that HT use had plummeted. Thus, the decrease in breast screening, may have resulted in a decrease in the discovery of breast cancer cases.

Increased breast density is a recognized risk factor for breast cancer. Whether hormone therapy which is known to induce changes in breast density also alters breast cancer risk is unknown.

Brain : ET/EPT has been shown to have a positive effect on **mood and behaviour** but there is insufficient evidence to support its use for the treatment of depression. There is no evidence of substantial cognitive decline over the menopausal transition, although factors such as fatigue, disrupted sleep, mood changes may adversely affect **cognitive functioning** in some women. Cognitive benefits have been shown with ET use after premenopausal oophorectomy. ET/EPT is ineffective in treating **memory loss or dementia** in older women (>65 yo) or in those with established Alzheimer's Disease. Whether or not a window of opportunity exists during the menopausal transition to prevent cognitive decline and/or AD with ET/EPT (as suggested from observational studies) remains to be determined. At this time, *HT cannot be recommended at any age for the prevention of cognitive aging or dementia.*

Both the WHI and earlier observational studies have shown that, ET/EPT when begun soon after menopause and before age 60, reduces **total mortality** by 30%.

Current opinion holds that women with early loss of ovarian function either as a result of **premature ovarian failure or surgery**, while at reduced risk for breast cancer have a significantly increased risk of osteoporosis, cardiovascular disease and early mortality and therefore should receive E/EP replacement therapy.

CONCLUSIONS:

Differing cultural and social attitudes as well as medical needs influence the requirements of women transitioning through the menopause. As at any age, the benefits and risks need to be evaluated. ET/EPT is safe and should be considered as first line therapy in the management of the symptoms and needs of women in early menopause. Clear benefits exist also for treatment of older women (>60 yo). For each woman who contemplates ET/EPT, the benefit:risk ratio needs to be established as it is unique to her, and it changes over time. Major determining factors include her age, pre-existing medical conditions, age at menopause, cause of menopause (e.g surgical, iatrogenic), time since menopause, other medications being taken, prior use/duration of ET/EPT and emerging medical conditions.

NAMS concludes ***"recent data support the initiation of HT around the time of menopause to treat menopause-related symptoms; to treat or reduce the risk of certain disorders, such as osteoporosis or fractures in select postmenopausal women; or both. The benefit-risk ratio for menopausal HT is favorable close to menopause but decreases with aging and with time since menopause in previously untreated women[1]."***

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