REVIEW ARTICLE

Meandering through The New Science of Hormone Replacement Therapy

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Ongoing progressive research at the clinical, experimental, molecular biological, and genetic levels has resulted in a radical change in thinking. A new science of tissue selectivity of the various gonadomimetic agents has evolved.

No other form of Hormone Replacement Therapy (HRT) has been reevaluated and rediscovered as much as conjugated equine estrogens (CEE). Additional benefits have been defined recently. However, it is imperative for those interested in this field to understand the molecular basis of action, as well as be aware of the broad range of action of HRT. This information would help appreciate the individuality of actions of different estrogens and progestogens in different tissues. In turn it would translate into effective, well-tailored prescription writing for individual patients. And that is what the practice of good medicine is all about.

To consider a well researched form of HRT, what better to study as an example than CEE when looking for various sites of action. Almost six decades of safe use by millions of women worldwide has firmly established the unquestionable supremacy of conjugated equine estrogens (CEE) in the clinical arena of menopausal medicine-and now research is unveiling the various previously unknown benefits of HRT.

Composition of Conjugated Equine Estrogens (CEE)

Research has shown that traditionally used conjugated equine estrogens contain not just estrogens but also progestogens and androgens- and that they contain more than 200 different steroids. In fact, 35-40% of the components are yet to be fully characterized. The contents are a combination of estrone sulfate, equilin sulfate, 17-a-dihydroequilin sulfate, 17-a-estradiol sulfate, 17-b? estradiol sulfate, and ??8,9-dehydroestrone sulfate (??8,9, DHES) amongst others. Estradiene is the newest and fourth most abundant estrogen that has been found with effective classic estrogen activity very similar to that of ? 8,9, DHES ? (1).

It is important to remember that affinity and biological potency of the various components of CEE are not necessarily equivalent. Comparing affinity with biological potency has produced surprising results. For example, ??8,9-dehydroestrone has 1% the binding affinity of estradiol, but it exhibits high potency. Hence binding affinity is not the primary predictor of biological activity. Moreover ??8,9-dehydroestrone comprises only 3.5% of the total estrogens in CEE. However, it makes up 15.4% of the total estrogens in circulation and has significant potential for biological activity because of its high bioavailability. Therefore all the various

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components of CEE contribute to the broad range of its effect in the female body.

Tissue Selective Mechanism of Estrogen Action

The mechanism of action of estrogens has been re-looked at. Recent research (2) has shown that estrogens manifest their biological activity through at least two distinct receptors - ER alpha (the original) and ER beta (the newly discovered receptor).

These receptors have different cellular distributions and therefore different actions. Though somewhat similar in structure- the ligand binding domain on the two receptor types is very different. Different estrogens have different ligand binding affinities. The potential benefits of an ER-beta selective ligand is that it is CNS selective and hence beneficial for Alzheimer's disease and cognition as well as for the endothelial cells of the cardiovascular system.

Different estrogens drive the estrogen receptors into different shapes after binding which is central to steroid receptor activation (3). Hence when ligated also, the active ligand/ receptor dimer complexes have different shapes. Thereafter the ligand/receptor complex binds to adapter proteins to form a gene promoter complex that is different in different cell types. Because the ligand receptor shapes are different, the adapter proteins into which they fit or bind with are also different. Each target cell (as in the brain, bone or uterus) therefore is uniquely positioned to respond to different compounds. Once the dimer has bound with the adapter, it enters the target gene resulting in the synthesis of the special protein by the cell. Different proteins are synthesized depending on the different 'fits' received into the genes. Hence the estrogen receptor ligands differentially affect transcription in different tissue cell types (4). In essence, steroid hormone receptors are ligand-dependent transcription factors that affect cell function. Classification of compounds as agonists or antagonists is tissue/cell dependent (5). The new science of estrogen action supports the concept that different estrogens acting through the same receptor can induce different biological activity.

The mechanism of estrogen action is not the same in all cells. It has therefore been possible to develop tissue selective estrogens (6).

Evidence is also emerging that estrogen, in addition to acting via receptors, can rapidly influence the physiology of the cell through other nongenomic mechanisms. The implication again is that no two estrogens act the same (7).

To simplify molecular jargon into clinical relevance, the take home message is that different estrogens acting through the same receptors can induce different receptor conformations resulting in different biologies and hence different effects on the various tissues of the female body (8-11). Remember whilst prescribing that all estrogens are not equal. Some are more equal than others! It also depends on the action or effect you're looking for in your patient. Do you want estrogenic effects on urogenital tissues only and are not 'fussed' whether it is cardio-&-osteo protective as long as it doesn't have any effect on the breasts, or do you want osteoprotection and/or cardioprotection as well?

Osteoporosis and newer benefits of osteoprotection

Estrogens and your bones are old friends. The osteoprotective benefits of estrogen replacement therapy are well established. The earlier a woman is started on HRT the better, as more osteoprotection is achieved by early initiation of therapy. Delaying the start of HRT to nine years after menopause increases the odds ratio for hip fractures to 0.62 (0.33-1.18) from 0.35 (0.24-0.5) in current users as shown by the Swedish Hipfractu

Study Group (12). However, it has now been shown that it is never too late to initiate HRT. A 4% increase in bone mineral density (BMD) with HRT has been demonstrated in elderly women (over age 65) started on continuous low dose CEE (0.3 mg/day) combined with 2.5 mg proxy progesterone acetate (13). This is a larger response than is typically seen with early menopausal women (50-55 years).

An enhanced effect on BMD has been demonstrated by combining CEE with biphosphonates (14).

HRT protects against osteoarthritis. Less risk of osteoarthritis has also been seen with current HRT use longer than 10 years in duration (15).

Alveolar Bone and Tooth Loss

Remarkable sophisticated studies have revealed that HRT reduces alveolar bone loss and tooth loss. Although the prevention of periorodontal disease is the most important factor in maintaining teeth, it has been hypothesized that some tooth loss may occur as a result of resorption of the alveolar bone and therefore may reflect osteoporotic bone loss. The strongest evidence of HRT benefit against tooth loss comes from a prospective study of 14-171 women in the Nurses' Health Study where the relative risk (adjusted for age and smoking) for tooth loss amongst current estrogen users was 0.76 (0.72-0.80). This protection disappeared with time after discontinuation of HRT (16). There is some evidence that BMD in post-menopausal women is correlated with the number of teeth (17-19).

Studies also suggest that estrogen may provide protection against tooth loss and periodontal disease in both past users and current users (16,20-22). One study that examined estrogen deficiency as a risk factor for periodontal disease involved 412 women (236 postmenopausal, aged 50-74 years and 176 perimenopausal, aged 25-49 years). The postmenopausal group included 59 ERT users Because cigarette smoking is the single most significant risk factor associated with severity of periodontal disease, only nonsmokers were included. Only 6.3% of the premenopausal women and 11.9% of the postmenopausal women using ERT had severe attachment loss, compared to the 18.6% of the non-ERT women (23).

Estrogen Benefits on Vision Disorders

You're thinking "Vitamin A maybe...but estrogens and my eyes??" Yes, it is true. A number of ocular symptoms may be observed and can be associated with the very onset of menopause itself. An example illustrating this is a study of 1287 women who visited a menopause clinic for relief of a variety of complaints. These women were questioned about ophthalmic symptoms. Four hundred and thirty (35%) of these women reported problems with their eyes that were associated with the onset of menopause. Out of the 19 reported ophthalmic complaints, the two most common problems noted were deterioration in visual acuity and dryness. Ninety eight women underwent ophthalmic examination and received cyclical HRT for 3 months. A significant imrpovement or complete relief from opthalmic complaints was reported by most of the women who were followed up by the end of three months.In addition to this, increased lacrimal fluid, and improved convergence and fusion (which is denotative of improved visual acuity), was objective evidence of improvement noted by a physica. examination (24).

Results from the Beaver Dam Eye Study indicate a slight protective effect of estrogen exposure on the female lenses. Nuclear sclerosis is associated with women who had a younger age of menarche and a decreased risk of cortical opacities is associated with an older age of menopause. The odds scale ratio of this study indicates that current use of ERT is allied with a less risk of more severe nuclear sclerosis. It has also been illustrated that

the longer the duration of ERT, the less the severity of the disease (25) .

Such strong correlations were not found in terms of a connection between estrogen and prevalent cataracts (nuclear, cortical and posterior subcapsular) in an evaluation of data from the Blue Mountains Eye Study (Australia). No association in any of the women was found between HRT and cataract. However, for HRT users of 65 and above, the odds ratio (OR) for cortical cataract was 0.4 (0.2-0.8). The OR for posterior subcapsular cataract was 2.1 (1.1-4.1) for current HRT users who had nonsurgical menopause (26).

The protective effect of estrogen on lens transmittance among postmenopausal women is indicated by the observation that lens transmittance was significantly higher in estrogen users and lens autofluorescence was significantly lower (27).

Estrogen has also been reported to reduce glutamate toxicity which is a significant contributor to glaucoma. A review article evaluating the hormonal regulation of intraocular pressure (IOP) found copious studies showing a small decline in IOP with ERT. Initially glaucoma was thought to be caused by increased but 1 in 6 cases has normal IOP. Recent data which points at glutamate toxicity as one of the major contributors to glaucoma promotes the notion of the protective role of estrogen against glutamate toxicity and hence glaucoma. At the molecular level, glutamate (an excitatory neurotransmitter) promotes rapid firing in nerve cells. If excess glutamate is produced, nerves are stimulated 'to death.' If glutamate does indeed(as data suggests) underlie the pathology of glaucoma, estrogen may provide menopausal women a benefit by protecting against glutamate toxicity (28-33).

One of the most important causes of visual loss, particularly in middle age, is central retinal vein occlusion (CRVO). The risk factors for CRVO in 258 patients with vein occlusion was examined by the multicenter Eye Disease Case Control Study Group (with 1142 controls). The results report that there was a significant ($p=0.001$) decrease in the CRVO risk with both former and current use of postmenopausal estrogen. However, an increased risk was found with systemic hypertension, diabetes, and glaucoma.

The most current study from the same Eye Disease Case Control Study Group above, examined risk factors among 198 women with idiopathic macular holes (IMH) with 1023 controls. The results illustrate that there is a significant decrease ($p=0.04$) in IMH in women who used HRT (34).

Yet another disease that may benefit from estrogen use (the list seems endless!) is age related macular degeneration (AMD). The evidence of the association between menopause and AMD is found in a Rotterdam study where results indicate that women with a younger age at menopause had a 90% increased risks of exhibiting signs of late AMD compared to women who had a later menopause. The data in this study is from a large case-controlled study of end-stage of disease and suggests that HRT reduces the risk of AMD developing. Other evidence supporting the slight reduction of ERT of early and late stages of AMD comes from smaller studies such as the Beaver Dam Eye Study (25).

Emerging Facts and Figures about Colon Cancer

Our third stop of the seemingly never-ending benefits of ERT/HRT is at the Colon Cancer junction. In a nutshell, the risk of colorectal cancer is prevented/ largely decreased by estrogens. This concept that postmenopausal HRT may decrease the risk of colorectal cancer justifiably received much attention considering that colon cancer is the third leading cause of cancer incidence and cancer deaths in women. Its incidence rises

at age 40 and is maximum between the ages of 60-75 years and is noticeably more common in women. Around 20 epidemiologic studies have been published examining the newly discovered relationship between HRT and decreased risk of colorectal cancer. And a majority of these studies indicate an inverse, protective effect of HRT on this cancer, particularly with current use (35-47). One of the largest studies found that whether current or former, the duration of estrogen use increased the protective effect. At the molecular level, the precise mechanism as to how estrogen might reduce the risk of colon cancer is still unknown. It has been hypothesized that it either promotes tumor suppressor activity through estrogen receptors or that it affects bile acid metabolism (48,49). The take home message is that estrogen reduces the incidence (up to 50%) and the mortality from colon cancer. It has also been known (along with aspirin) to reduce the incidence of adenomatous polyps. The highest reduction in risk is observed for tumors of the proximal colon. The control for screening has not eliminated an inverse association. Recent studies of colorectal polyps and hormone use do not support a screening bias. Epidemiologic evidence does support the fact that HRT both lowers the risk of colorectal polyps and inhibits promotion of existing cancers.

Estrogens are Cardioprotective

Long term research into CEE use and cardiovascular disease has established its role for primary cardioprotection in preventing cardiac morbidity and mortality in normal and at risk women. The recent HERS study has cast a shadow on its role for secondary cardioprotection in women with already established cardiac disease.

Both the HERS and the Nurses Health Study have demonstrated an increased risk of cardiac morbidity and mortality in the first year of ERT use, particularly in the first four months. However, they have both shown that there are apparent long term benefits with a decreasing risk of cardiovascular disease with increasing duration of use of HRT. Some issues need to be considered and clarified. It takes time for the process of atherosclerosis to arrest and regress. It was also likely that the placebo group were more likely to be prescribed statins because their lipids were not settled as with CEE. So, was the HERS an HRT versus Statin study instead of HRT versus placebo study? The increased risk of major coronary events within one year of HRT use was seen in women with prior MI within a year of starting HRT (relative risk 2.19 compared to relative risk of 0.49 in women with a prior MI more than two years before starting the HRT). This information could perhaps be extrapolated in the future to using HRT after one or two years of an attack of myocardial infarction. This early risk has not been seen in the ERA trial.

Several secondary prevention studies show results where ERT use in women reduces the risk of mortality by 50%-90%. This degree or reduction is marked and is comparable to that observed following successful treatment of LDL cholesterol elevations (50-54). Two studies involved estrogen use in postmenopausal women with angiographically defined coronary artery disease (CAD). Women using estrogen had significantly less coronary artery stenosis as compared to those women not using estrogen. Patients with the most advanced CAD benefitted the most from ERT usage (55-56).

In relation to restenosis and angioplasty outcome, the effects of HRT are not constant. Interestingly, two studies present contradictory outcomes. In one, a reduction by 50% was seen in restenosis rate following atherectomy but not following angioplasty (57). Another study showed a highly significant long term benefit in the 7 year mortality, although no effect was seen on the occurrence of myocardial infarction after angioplasty (58).

Novel Anti Inflammatory and other Actions of CEE on the Brain

More important than your heart? Perhaps the brain that controls it. And yes, estrogen has its beneficial actions here too. In the animal model, CEE has a protective effect against-amyloid-beta-induced inflammatory reaction in Alzheimers disease (AD). The decrease in prevalence of AD in women on ERT may be partially explained by modulation of the normal age related increase in cell membrane breakdown and decline in seratonergic function. Women taking HRT have milder symptoms than those who do not. HRT decreases the risk and delays the onset of AD. The use of estrogen for longer than 1 year reduces the risk of developing AD by 5% annually. Estrogens have also been shown to improve verbal and visual memory.

Several recent epidemiological studies provide the best evidence relating estrogen deficiency to AD. A 40-60% reduction in the risk of AD in women who have taken ERT has been demonstrated individually by each of the 5 independent studies. It must also, however, be noted that the majority of these hormone users received unopposed estrogens (59-63).

With the loss of estrogen at menopause, it is hypothesized that a selective neuronal loss within the hippocampus (a region of the brain which subserves memory, that is uniquely sensitive to hypoglycemia as evidenced by autopsy studies of insulin dependent diabetics) results from a decrease in estrogen dependent glucose transport to the CNS.

To Tie It All Up

The new science of Hormone Replacement Therapy has clearly defined the benefits associated with its use. The increase in the risk of breast cancer when seen in perspective is small. The final decision whether or not to take even this small risk versus all the benefits must lie with the woman who is considering taking the therapy. What should be reassuring to know is that hormones for estrogen deficiency have been in use for years and no other compound has had the quality and quantity of research as conjugated estrogens. Over time, not only obvious symptomatic relief is provided to women, but there are also the subtle, unseen indirect advantages to her entire body as have been shown. What is amazing is that everyday with greater in depth research, more is being uncovered. No matter what, with estrogens you're definitely on a winning horse!!

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