Why HRT and Anti-Aging Medicine?

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• 1942 FDA approves estrogen for menopausal symptoms 21 years before the first randomized control trial of estrogen replacement therapy
• 1968 Robert A. Wilson “Feminine Forever” book is published, which initiated a tremendous marketing opportunity for the pharmaceutical industry to promote synthetic HRT
• 1984 NIH adds osteoporosis as an indication for HRT

HRT Story
Summary of the HRT
Highlights
• 1990 Premarin becomes the #1 selling drug in the US
  Wyeth Ayerst asks the FDA to approve Premarin for
  the prevention of heart disease….petition is denied
• 1990 Nurse’s Health Study shows 36% increase in
  breast cancer among current hormone users (Colditz
  et al., JAMA. 1990;264(20):2648-53
• 1993 NIH under direction of Bernandine Healy
  approves the WHI and patient selection begins
• FDA denies permission for generic Premarin because
  it is impossible to clearly define it’s contents

HRT Story
History of HRT highlights
HRT Story

History of HRT Highlights

• 1998 HERS 1st large RCT of HRT and CHD in menopause is published (Hully et al., JAMA 1998 Aug 19;280(7):605-13
• 2000 Preliminary findings of WHI suggest similar early CHD risk
• 2001 American Heart Association reverses its recommendation to take HRT for CHD
• July 3, 2002 HERS 2 trial shows no evidence of late benefit of HRT for CHD but does show 40% increase in VTE and GB disease (Grady et al., JAMA;288(1):49
• A large amount of literature stating HER prevented postmenopausal bone loss

• Recent meta-analysis showed a significant reduction in non-vertebral fractures though less in women >60 (Torgenson et al., JAMA 2001;285(22);2891)

• ……evidence about the efficacy of postmenopausal estrogen for prevention of osteoporotic fractures is weak… Until the effectiveness of estrogen is clarified, treatments other than estrogen should be the first choice for older women in osteoporosis.” (Grady and Cummings, JAMA. 2001 Jun 13;285(22):29

HRT Story
History of HRT Highlights
• Jan 2000 Combined HRT is worse than ERT in terms of breast cancer risk
• Feb 2002 Increased risk of breast cancer with HRT
• July 9, 2002 NIH halts WHI
• July 17, 2002 WHI publishes its first findings
• July 17, 2002 study hits the media!
• Wyeth Ayerst Stock plummets
• Law firm of Schiffrin and Barroway files class action against Wyeth Ayerst

HRT Story
History of HRT Highlights
• What do the patients want?
• Premarin is not a bioidentical estrogen
• There are different types of estrogen and each confers different effects on gene expression “Estrogens have widespread biological actions and there are naturally occurring phytoestrogens that mimic some of the actions of endogenous estrogens. In this review we will focus on new biochemical and molecular aspects of the actions of estrogens as well as clinical and physiological influences [of their metabolism]”. N Engl J Medicine 2002; 346:340

So Where Do We Go From Here?
• Numerous studies on estriol safety exist

• Abstract: examine risk of breast cancer after noncontrceptive treatment with estrogen, a prospective study of 23,244 women 35 yrs of age or older who had estrogen prescriptions filled in the Uppsala region of Sweden

• Findings: 10% increase in the relative risk of breast cancer in 23,244 women for whom estrogens were prescribed for symptoms of menopause

• “We found no association between weaker estrogens (mainly estriols) and the development of breast cancer.”

• Available review of 150 articles found via searches using PubMed and Medline OVID. Of these 150 articles references were selected deemed most clinically relevant.

• Reviewed 35 articles felt most relevant to clinical practice concerning the safety and efficacy of estriol. It is no a comprehensive listing of available studies. Interest to note that a majority of the studies were conducted outside of United States particularly in Japan and Western Europe.

Evidence Bioidentical HRT
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- Articles included are those which show:
  - Oral and vaginal estriol is not associated with increased risk of breast cancer
  - Estriol is safe for use in postmenopausal women previously treated for breast cancer
  - Estriol prevents bone loss and increased bone mineral density in postmenopausal women
  - Oral estriol does not cause endometrial changes in postmenopausal women
  - Estriol is effective in the treatment of atrophic vaginitis
  - Estriol is safe and effective for the treatment of climacteric symptoms in postmenopausal women
  - Vaginal application of estriol is systemically absorbed
Evidence Transdermal Efficacy of Bioidentical HRT

- Newly released Estrogel (estradiol gel) by a Pharma company

- Reference: Percutaneous 17B-estradiol gel for the treatment of vasomotor symptoms in postmenopausal women David F. Archer MD et al, Menopause (The J of the N American Menopause Society) Vol10 No.6 2003

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• Bioidentical hormones are identical to hormones produced endogenously and molecularly identical. These include estrone (E1), estradiol (E2), estriol (E3).
• Also include progesterone (P4)
• Also include testosterone

• E2 is the most physiologically active form of estrogen. Synthesized in the ovaries and metabolized in the liver.
• E1 is converted reversibly from estradiol in the liver and small intestine. Increases after menopause when the adrenal glands play more important role than ovaries in hormone synthesis.
• E3 remains intact and does not convert to E1 or E2.
• Progesteron, Progestins, Progestogen are not the same
• Progesterone refers to a single molecular structure bioidentical to what the body produces.
• Progestogen is category of hormone molecules both natural and synthetic that act like progesterone in the uterus
• Progestin generally refers to synthetic progesterone
• Progesterone originally was obtained by extraction methods from animal placenta
• Now produced in laboratory from saponins found in soy or from wild yam.

What is Bioidentical HRT
• Progestins mimic the body’s progesterone to bind progesterone receptor sites but do not deliver the full range of hormone message signals like natural progesterone.
• Synthetic progestin may have similar effects on the endometrium but confer different action elsewhere i.e. brain, mineralocorticoid receptors, etc.
• These different progestins have been mapped to affinity to androgen, progesterone, glucocorticoid, estrogen receptors.
• 19-nortestosterone derivatives are known to have estrogenic properties (could be attributed to their estrane structure, an 18 carbon tetracyclic hydrocarbon nucleus that is the parent structure to all estrogens.)
• Sufficient evidence to suggest pulsatile delivery of estrogen and progesterone that occurs naturally enhances function of these hormones in the body.

• In theory continuous application of hormones may down-regulate receptors hence decreased activity of these hormones.

• Reduced dosage would imply decreased likelihood of unwanted side effects as well as reduced impact on the liver due their metabolism thru the liver.

Differences in BioHRT Delivery
• Oral
• Transdermal (patch)
• Percutaneous (creams, gels)
• Intramuscular
• Sublingual
• Vaginal (gel, cream, ring, supp)
• Pellets
• Nasal

Routes of administration
• Same doses percutaneous vs vaginal (greater circulating blood levels vaginally of estrogens and progesterone)
• Percutaneous, transdermal and vaginal less metabolism to E1
• Oral progesterone: 90% metabolized by first pass effect of liver (shunting thru enterohepatic circulation) and increase in 5-alpha metabolites, deoxycorticosterone, deoxycorticosterone sulfate, beta-pregnenolone.

Routes of administration
BioHRT
• Progesterone and its metabolites differing effects on brain, uterus, smooth muscle and oocyte:
• Depressive effects attributed to pregnane metabolites

Routes of administration
BioHRT
• Hot flashes/vasomotor flushing due to lack of estrogen
• Progesterone can have beneficial benefit
• Study pub Obstet Gynecol 1999;94:225-28
  • using progesterone cream topically resulted in significant reduction in number and intensity of hot flashes in 83% or participants and benefits in “quality of life” measurements
• Study pub Blood 2004:104-16 subjects received 20mg of progesterone cream topically daily x4wks significant improvement of menopausal symptoms measured by Greene Climacteric Scale scores.’

Effects of BioHRT on Menopausal Symptoms
• Study (pub Menopause 2001;8:10-16) compared effects of CEE with MPA to CEE with OMP in postmenopausal women. Latter group significantly improved quality of sleep over synthetic progestin group.

• Study (pub Clin Ther 2001;23:1099-1115) compared MPA to OMP. Found OMP better tolerated and additional benefits in cognition and improvement of menstrual problems.

• CEE (conjugated estrogens)
• MPA (medoxyprogesterone acetate)

Effects of BioHRT on Menopausal Symptoms
Effects of BioHRT on Menopausal Symptoms

- Estriol demonstrated to reverse vaginal atrophy
- Estriol dosing is much higher than estradiol to achieve similar effects in reducing hot flashes and vaginal dryness in menopausal women
- Estriol typically doses twice daily to achieve steady state levels
• Recent study published in Blood 2004 studying progesterone cream for safety and efficacy found no markers for inflammation or clotting.

• Study also found in women with higher than normal cortisol levels there was a marked decline in the level of cortisol to normal range while using progesterone cream vs placebo.

Hemostatic Effects of BioHRT
• In the Postmenopausal Estrogen and Progesterone Intervention (PEPI) Trial
• OMP did not negate the beneficial effect of estrogen on HDL significantly more than MP.
• Mention here that 3rd generation progestins such as norgestin and desogestrel have not demonstrated the same adverse effects on lipids.
• MP’s increase severity of atherosclerosis in coronary arteries, suppress protective effect of estrogen on arterial injury, increase insulin resistance, decrease beneficial effect of estrogens on vasodilation.
• Consistent with the fact that synthetic estrogen and 19-nortestosterone can result in decreased glucose tolerance.
• Glucose tolerance unaffected by P4

Effect on Lipids with BioHRT
Two animal studies comparing E2 with P4 vs E2 and MP:
- E2 with P4 protected against coronary hyper-reactivity and coronary vasospasm
- E2 with MP increased coronary hyper-reactivity and coronary vasospasm

Another study
- P4 reduced risk of atherosclerosis by inhibiting vascular cell adhesion molecule-1 (VCAM-1). MP did not.
- P4 with 17-beta E2 both inhibited cardiac fibroblast growth. Effects of 17-Beta E2 enhanced by P4. suggests this combination may protect postmenopausal women against CAD risk.

CAD risk with BioHRT
• Normal liver function essential for lipid metabolism.
• Regards to estrogen: comparison between ethinyl estradiol EE and estradiol E2 showed EE had greater beneficial effect on lipids than E2 but:
• EE marked increase in liver protein synthesis inclusive of SHBG, PZP markers of increased estrogenic effect
• P4 has demonstrated safety on its effects on lipid metabolism and hemostatic effects in all routes of administration.

CAD risk of BioHRT
• Conventional estrogen replacement therapy is known to increase the risk of blood clots. High dose estrogens and oral estrogens increase liver protein synthesis including coagulation factors.

• Oral estrogens known to increase angiotensin which can increase BP and stroke risk in susceptible women.

• Randomized crossover study estriol did not effect hemostatic function wheras ethinyl estradiol decreased prothrombin time while increasing plasminogen and factor VII. In the WHI study CEE with medoxyprogesterone was shown to increase blood clotting events.

**Thromboembolic effects of BioHRT**
• Anti-mineralocorticoid activity of bioidentical progesterone: antagonizes aldosterone hence increased urinary sodium excretion hence may reduce BP in some hypertensive pts. This ant-mineralocorticoid effect not seen with synthetic progestins.

• Normotensive patients bioidentical progesterone can decrease vascular sympathetic tone without comcomitant drop in BP.

• Bioidentical progesterone acts via nitric oxide pathway to enhance vasodilation and improve microcirculation.
• Large French cohort study published Cancer Detect Prev 1999 (vol.23)

• 1150 women with benign breast disease showed no increase in breast cancer risk with women using topical progesterone cream, common European treatment for breast mastalgia.

• In addition researchers noted decrease in breast cancer risk (RR=0.8) in women using P4 cream plus oral progestogen compared with women using progestins alone (RR=0.5).

Effect of BioHRT on Breast
• Two recent studies difference in breast cancer risk when comparing synthetic progestins to P4 as part of the HRT regimen.
• French cohort study 3175 patients pub Climateric 2002;5:332-40 showed:
• Postmenopausal women using natural HRT (83% used transdermal estradiol and non-MP progestogens found no increased risk of breast cancer in these users.

Effects of BioHRT on Breast
• French E3N-EPIC cohort study published Cancer 2005;114:448-54
• Most significant examination at the differences in progestogens and breast cancer risk
• Assessed risk of breast cancer associated with HRT use in 54,548 postmenopausal women
• Found risk significantly greater (p<0.001) with HRT containing synthetic progestins (RR=1.4(1.2-1.7)) than with HRT containing micronized progesterone (RR=0.9(0.7-1.2)).
• Realize these are not prospective trials looking at the safety of bioidentical progesterone relative to breast cancer risk but do provide promising evidence for safety of bioidentical P4.

Effects of BioHRT on Breast
• With respect to estrogens and breast cancer risk
• Most important consideration is the susceptibility for abnormal estrogen metabolism due to liver biotransformation dysfunctions
• Leads into discussion of liver detoxification pathways
• Emphasizes importance of individual variation and biochemical differences

Effects of BioHRT on Breast
• Bone turnover increases at menopause and may remain high for 25 or more years following the last menstrual cycle
• Combination of estrogen, progesterone, testosterone, corticosteroids, vitamin D, thyroid hormones, and retinoids
• Stand alone estrogen replacement therapy beneficial effect on limiting bone loss and reducing incidence of fractures
• Stand alone progesterone replacement studies are mixed. Benefits through it effect on the proliferation and differentiation of human osteoblasts. Double blind placebo controlled studies on humans have yet to demonstrate significant increase in bone mineral density BMD or reduction in fracture rate.
• Several studies looking at estrogen and progesterone show synergistic effect to increase BMD
• Testosterone can also decrease urinary calcium loss and bone resorption
• Bioidentical progesterone numerous beneficial effects on brain and nervous system
• Supports myelin formation
• Activates GABA receptors
• Reduction of brain ischemia and inflammatory response after traumatic brain injury
• Synthetic progestins do not have same physiological benefits
• WHIMS found equine estogen plus synthetic progestins doubled risk of developing dementia in women 65 and older
• WHIMS (Women’s Health Initiative Memory Study)

Effects of BioHRT on Brain
Effects of BioHRT on Brain

- Estrogens known physiological effects on brain
- Improved blood flow via vasodilation
- Stimulation of serotonin and norepinephrine neurotransmitters which impact nerve cell function and mood
- Atherosclerosis Risk in Communities (ARIC) study evaluated the effects in 2,000 women of estrogen on memory and cognitive function, participants 48-67, 10 yr period, found no correlation (either positive or negative) between estrogen and cognitive function. This study did not denote which estrogens were used.
- WHIMS study also failed to demonstrate cognitive benefit for estrogen replacement therapy alone. In fact, demonstrated increased risk for dementia in women using estrogen alone, although not as great risk as combined synthetic HRT. This study used equine estrogens with and without MPA.
• Bioidentical HRT is well tolerated
• Provides symptom relief
• Can address many of the health needs as well as individual preferences of menopausal and perimenopausal women
• Testing of hormones before initiation of therapy
• Quality of compounded hormones extremely important
• Improved quality of life

Conclusion of BioHRT
• Gene expression defines aging
• Genotype/SNP’s
• Anti-aging slows aging process
• Treat the cause
• 7 basic clinical concepts of aging
• Mitochondrial Dysfunction
• Inflammation
• Excess free radicals/oxidative stress
• Excess methylation
• Insufficient supply of repair blocks
• Glycation
• Hormone imbalances inc. insulin cort decreased thyroid sex hormones melatonin gh, resulting poor signaling and cell turnover maintain balanced
• Compromised DNA integrity p53 indicator of aptosis in body due to comb of inc dna damage
• Telomere Length

Anti-Aging Medicine