Goldilocks and the Three Estrogens: Menopausal Hormone Replacement in 2012

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Objectives

- Assess benefits and risks of treatments for menopausal symptoms, including cognitive behavioral therapy, physical exercise, supplements, and hormone therapy.
- Apply hormonal and nonhormonal evidence-based strategies to manage menopausal symptoms.
- Construct a risk-benefit profile for patients considering a hormone therapy regimen that includes consideration of personal risk factors, such as venous thrombosis, CHD, stroke and breast cancer.

QUESTION #1

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  - A. one per ten thousand women per year
  - B. one per thousand women per year
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  - D. 30 percent
QUESTION # 2

WHAT ARE BIOIDENTICAL OVARIAN HORMONES?

- A. steroids from ground up women’s ovaries
- B. steroids from pregnant mare’s urine
- C. steroids from ground up Mexican yams
- D. steroids that can be measured by standard RIA
- E. Phystoestrogens from redclover and soy beans

Question # 3

A patient with VMF states she has heard that soy can decrease flushes. What is the most ethical response?

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NORMAL DEPLETION OF OOCYTES

A. OVARIAN FOLLICLES AT 7 YEARS OLD
B. OVARIAN FOLLICLES AT 20 YEARS OLD
C. OVARIAN FOLLICLES AT 30 YEARS OLD
70 Years of MHT

- Injectable equine estrogens for young women symptomatic from oophorectomy in late 1930’s and early 40’s
- Oral conjugated estrogens in the 50’s and 60
- Estrogens balanced by cyclic progestins in the 70’s and 80’s
- Continuous combined estrogens and progestins in the 90’s
70 Years of MHT Research

- Case series in the 40’s and 50’s
- Retrospective studies in the 60’s and 70’s
- Prospective cohort studies in the 70’s and 90’s
- Prospective Randomized Trials in 90’s and 2000’s

We think we know what we thought we knew

- MHT is highly effective for menopausal vasomotor flushes
- ET is the highly effective treatment for symptomatic vaginal atrophy
- MHT/ET is very effective in decreasing the risk of postmenopausal osteoporotic fractures

We think we know what we thought we knew

- MHT/ERT attributed thromobembolic events are rare (1/1000/year)
- MHT attributed breast cancers are rare (1/1000/year) and no increase with ERT in WHI
- MHT/ET attributed coronary artery events are NOT increased in the original target population of postmenopausal women (the symptomatic young women who we treated)
What we think we know really only applies to Caucasian Americans
- Women’s experience in menopause varies greatly from woman to woman and culture to culture and “race” to “race”
- African American women are more likely to be troubled by hot flushes – osteoporosis is uncommon
- Middle Eastern women are more likely to have joint discomfort as the most likely symptom
- Asian women have fewer flushes, more headaches
- Mayan women don’t complain much

The Women’s Health Initiative

IF THEY ONLY HAD A HEART

HRT AND SUZANNE SOMERS

IF SHE ONLY HAD A BRAIN
What are CLEARLY (mostly) symptoms related to estrogen withdrawal?

- Hot flushes/night sweats
- Vaginal Dryness

PERIMENOPAUSE

Hormone Levels Are Futile

MHT and Sexual Function

New Dosing

- MHT/ET is very effective in treating dyspareunia due to vaginal atrophy
- For otherwise asymptomatic women, vaginal estrogens given twice a week treats atrophy without significant systemic side effects or risks
- 10mcg pill, ½ gram cream is new effective dosing
- MHT/ET is not recommended or effective for other problems of sexual function
WHAT'S NORMAL?

NATIONAL HEALTH AND SOCIAL LIFE SURVEYS
Shiffren et al. Obstetrics and Gynecology 2008
**Total Satisfying Sexual Activity at 24 Weeks from PSFS**

<table>
<thead>
<tr>
<th>% Increase From Baseline</th>
<th>Placebo</th>
<th>Testosterone patch</th>
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<td>33%</td>
<td>74%</td>
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**p=0.0003**


**APHRODITE TRIAL**

- 814 women from centers in UK and Australia randomized to 150ug testosterone patch, 300 ug testosterone patch or placebo – 52 weeks
- Sexual satisfaction improvement only seen in 300 ug group (same as INTIMATE trial)
- 300 ug group was supraphysiologic in T levels and increase in unwanted androgen side effects
- 4 cases of breast cancer in treatment group, none in placebo group

Davis et al, NEJM, 2008
New Options Fail FDA approval

- Testosterone on hold for more safety data given limited improvement in libido over placebo
- Flibanserin fails approval for limited improvement and increased side effects
- Bremelanotide not moved forward because of hypertension though lower doses might be studied
- No new options currently on fast track
- [sigh]

Bremelanotide – early study 18 pts

The things that stop you having sex with age are exactly the same as those that stop you riding a bike (bad health, thinking it looks silly…no bicycle).

Dr. Alex Comfort
The Joy of Sex
Emotional intimacy
Sexual stimuli
Sexual arousal
Desire and physical satisfaction
Psychological and biological factors govern "arousability"

Female Sexual Response: Basson Intimacy-Based Model

Just get in the boat and row
Just get on the bike and ride

Dr. Jones’ Nike Recommendations

Just get in the boat and row
Just get on the bike and ride

(just do it)
MHT and Osteoporosis

- RCTs and WHI show decrease in osteoporotic fractures, including hip fractures with MHT
- Estrogen promotes “normal bone”
- Estrogen has a short half life in bone
- The bisphosphonate story is in flux – attributable risks of osteonecrosis of the jaw and spontaneous fractures are about 1/100,000 (that is low)
- Bisphosphonates have a very long half life in bone – drug “holidays” after 3-5 years are being
FLEX Implications

- Results from FLEX should reassure physicians that prolonged bisphosphonate is safe...and holiday is safe
- Consequences of discontinuation: modest bone loss. Increased risk of vertebral fraction but no increase in non-vertebral fraction
- Drug "Holiday"
  - Benefits vs risks – convenience and low cost with slight increase in vertebral fracture.
  - Consider if BMD is over -2.5 and no fractures

MHT and Diabetes

- WHI showed 21% reduction in incidence of Type 2 Diabetes
  - (15 fewer cases per 10,000 women per year)
- Meta-analysis date suggest that MHT is associated with improvement in insulin resistance in postmenopausal women
- (not a reason to initiate therapy – just a bennie)

Salpeter et al. Diabetes Obes Metab 2006

ET and WHI – no fuss

- No increase in ischemic heart disease (in fact a slight decrease in women 50-60)
- 30% DECREASE in breast cancer (not statistically significant)
- 1/1000 attributable risk of stroke (but only in 60-70 year olds, not in "young" women)
History of hot flashes and aortic calcification among postmenopausal women.
Thurston, Rebecca; Kuller, Lewis; MD; DrPH; Edmundowicz, Daniel; MD; MS; Matthews, Karen

Estrogen Therapy and Coronary Artery Calcification – WHI Estrogen Only Trial
1079 patients (50-59) equally randomized to CEE .625 or Placebo
Average 7 year followup – women who were at least 80% compliant

Cognitive Function
- May be defined by psychometric testing of memory or certain cognitive tasks
- May be defined by the patient as mood alteration, insomnia, anxiety, memory difficulties, word finding difficulties, or problems with concentration
- Hard to define but you know when your are losing it – but don’t know when you have lost it
Estrogen and the Brain: Support and Protect

- In the mature brain, estrogens support function
- Effect neurotransmitters, axonal branching, blood flow in adults
- Estrogen receptors present throughout the brain
- Effect the brains of women and men

Menopause and Cognition: Lifestyle

- Women who exercise regularly have better cognitive scores
- Prescribing exercise is hard to randomize and placebo control but some studies show a small increase in psychological tests, and reaction time
- Exercise does decrease stress and psychological distress which effect memory

Menopause and Cognition: Diet

- Antioxidants, phytochemicals
- Diet rich in antioxidants retards normal cognitive aging process and can enhance cognitive function in aging rats
- People who have diets rich in phytochemicals have better cognitive function
- (People who can choose their food have better cognitive function)
- Prescribing vitamins doesn't work
Menopause and Cognition: Stress

- Short term stress enhances memory
- Long term stress decreases hippocampal neurons in animals, and blood flow in humans
- Long term stress is toxic to memory – through direct effect on neurons, or by oxidative stress and corticosteroids

Declines in Verbal Memory With Estrogen Suppression

Mean Age, 34 Years

- Baseline
- Month 3 LAD only
- Month 5 LAD + Add-Back Treatment

*P < .05 compared with baseline.

Hot Flushes…how long will they last?

- Clinical guidelines suggest 6 months to two years
- Some research studies with a placebo arm found 50% reduction with placebo in 60 months
- Recent longitudinal studies show average of 5 years (s.d. 3 years, median 4 years)*
  - Only factor in this Australian study that was associated with duration was exercise – more exercise was associated with shorter duration of hot flushes.

* Col NF et al. Menopause. May/June 2009

Alternative Approaches

Limited Effectiveness

- Lifestyle changes, cool environment
- Vitamin E, dong quai, ginseng, evening primrose oil, and black cohosh – no difference compared with placebo
- Phytoestrogens – not clearly better than placebo
- Clonidine (patch or pill) – better than placebo but side effects
- Megestrol (progestins work best of all non estrogen options)
- SSRI/SNRI therapy (about 40% reduction)
- Gabapentin (about 40% reduction)

SSRI/SNRI = selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor.

MHT Risks: Numbers for the Patient

New MHT Starts in women 50-60

- One extra blood clot per 2000 women per year
- One extra breast cancer detected per 2000 women per year (no increase in estrogen only)
- No differences in deaths over 5 years between women who take MHT and women who don’t
MHT: Numbers for the Patient
Long term users

- The data regarding blood clots and myocardial infarction (from WHI and HERS) suggests that the risks are clustered in the first few years. Long term studies do not suggest increased risks increasing over time.
- One extra breast cancer detected per 100 women per 10 years of use.

HRT and Mortality

- WHI trials consistent with observational studies indicating that HRT may reduce total mortality when initiated soon after menopause.
- 30% reduction over course of study when data from WHI ET and HRT combined for women initiated before 60.
- (no significant difference over a lifetime, though).

Mayo Clinic Cohort Study of Oophorectomy and Aging

- 1091 bilat
- 1274 unilat
- 2383 controls
- Only for benign Conditions
- Only prior to menopause

Rivera et al, Menopause, 2009
HOW WOULD AN REI TAKE ET?

- Probably not oral (to decrease the very small risk of VTE – but difference not clinically significant)
- Transdermal patch
- Transdermal gel
- Transdermal cream
- Transvaginal ring
**WHAT IS ‘BIOIDENTICAL’?**

- Steroids that are identical in chemical structure to endogenous HUMAN estrogens – are equivalent in RIA assay
- Estrone (E1) – interconverted to E2
- Estradiol (E2) – Interconverted to E1
- Estriol (E3) – very low except in pregnancy – least potent of the three estrogens
- **But only E2 really matters**

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**How Would and REI Take Progestin**

- Hmm….that’s a tough one
- Probably progesterone (for limited improvement in lipid profile)
- Probably continuously (new data on very significant increase in relative risk of uterine cancer with long interval cyclic progestins (any less frequently than monthly is not frequent enough)
- **STAY TUNED: Progestin options will be increasing (new chemistry, new formulations )**

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**Endometrial Cancer: Estradiol-Progestins**

- Finnish Cancer Registry: 224,015 women who used estradiol-progestin therapy for at least 6 months
- Continuous therapy for 5 or more years – 76% reduction (10,759 women: 12 cancers observed, 33 expected)
- Sequential monthly progestin 5 years – 69% increase (25,582 women: 152 cancers observed, 90 expected)
- Sequential q 3 month progestin 5 years – 276% increase (3500 women: 65 cancers observed, 17
Progestin Frequency and Endometrial Cancer

Jaakkola et al, Obstet Gynecol 2009

Bleeding that predicts pathology?

Burch et al. Maturitas 2000

Amberen

- Ammonium Succinate
- Calcium Disuccinate
- Monosodium L-Glutamate
- Glycine
- Magnesium Disuccinate Hydrate
- Zinc Difumarate Hydrate
- Tocepherol Acetate
Alternative Therapies: Issues

- Aggressive marketing generates inquiries and use
- Side effects and drug interactions are not well known but clearly occur
- Providers should record these as medications
- Need for randomized, placebo-controlled clinical trials is imperative
- May have limited indications in very specific populations

NO NEWS IS GOOD NEWS

- THE NEWS YOU AREN'T HEARING IS MOSTLY GOOD NEWS

For All Women (and you guys)

- “Live in rooms full of light, avoid heavy food, be moderate in the drinking of wine, take massage, baths, exercise and gymnastics, change surroundings and take long journeys, strictly avoid frightening ideas, indulge in cheerful conversation and amusements, listen to music”

A. Cornelius Celsus
Physician, 1st Century AD
Lead a Purposeful Life
Recommended Reading:
Postmenopausal Hormone Therapy
An Endocrine Society Scientific Statement

JCEM Supplement July 2010

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