Menopause Therapy 2013: What’s new?

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Disclosure

- I am on the Speaker’s Bureau for Warner Chilcott. I have limited my presentation to evidence that is supported by peer-reviewed studies and will provide a balanced view of available therapeutic options, where applicable.
Menopause treatment 2013

- WHI, 10 years later
- KEEPS Trial 2012
- NAMS 2012 Hormone Therapy Position Statement
- STRAW +10
- Polymorphisms
What’s old?

- 100 yrs: Ovarian extract, venesection (never more than 100cc) and Lydia Pinkham’s
- 70 yrs: Premarin
- 40 yrs: OC
- 20 yrs: PEPI and low dose OC
- 10 yrs: WHI and transdermals
What is menopause?

- STRAW +10
  - Stages of Reproductive Aging Workshop.
  - Updated 10 yrs later
  - Healthy, non obese, nonsmokers

Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. Sioban D. Harlow, PhD,1 Margery Gass, MD, NCMP,2 et al for the STRAW + 10 Collaborative Group. Menopause, April 2012 Vol. 19, No. 4
Straw + 10 summary

- Menopause: 12 months since last spontaneous menses
- Few years +/- is perimenopause
  - Rapid changes in FSH and E2, symptoms
- FSH > 25 suggests few remaining receptive follicles ("late perimenopause") but doesn’t define menopause
Perimenopausal sxs

- Irregular bleeding patterns
- Vasomotor sxs
- Sleep disorders
- Anxiety/irritability
- Vaginal dryness/Dyspareunia
- Pregnancy
Treatment

- Education: It’s normal
- OC, DMPA (contraception, bleeding, symptoms)
- Mirena, hysterectomy (contraception, bleeding)
- Ablation, progestins (bleeding)
- Hormone Therapy (symptoms)
  - HT: general hormone therapy, estrogen + progestin
  - ET: estrogen alone therapy
Perimenopausal bleeding

- Transition from regular ovulation to irregular ovulation to anovulation.
- Normal and may take many years
- May or may not be an easy transition
- When is it pathological?
Perimenopausal bleeding

- Consider pathology
  - Heavy, prolonged, constant bleeding
  - Pregnancy, STD

- W/u with pelvic sono
  - Thick endometrium (no absolute definition)
  - fibroids, polyps
  - ovarian cysts, expected follicle activity
Perimenopausal bleeding

- Consider EMBx understanding limitations
  - Small sample size
  - Discomfort
  - Best when sample can be generalized to entire endometrium
  - Poor correlation w/ focal lesions

- Treatment as above
A Decade After The Women’s Health Initiative—The Experts Do Agree

The statement was published in the journals of The North American Menopause Society (Menopause), the American Society for Reproductive Medicine (Fertility and Sterility), and The Endocrine Society (Journal of Clinical Endocrinology and Metabolism)

A decade after the Women’s Health Initiative—the experts do agree Stuenkel, Cynthia A. MD, NCMP; Gass, Margery L.S. MD, NCMP; Manson, JoAnn E. MD, DrPH, NCMP; Lobo, Rogerio A. MD; Pal, Lubna MBBS, MRCOG, MSc, NCMP; Rebar, Robert W. MD; Hall, Janet E. MD

Menopause August 2012 - Volume 19 - Issue 8 - p 846–847
Endorsing organizations

- Academy of Women’s Health
- American Academy of Physician Assistants
- American Academy of Family Physicians
- American Association of Clinical Endocrinologists
- American Medical Women’s Association
- Asociación Mexicana para el Estudio del Climaterio
- Association of Reproductive Health Professionals
- National Association of Nurse Practitioners in Women’s Health
- National Osteoporosis Foundation
- Society for the Study of Reproduction
- Society of Obstetricians & Gynaecologists of Canada
- SIGMA Canadian Menopause Society
• HT is an acceptable option for treating moderate to severe menopausal symptoms in relatively young (up to age 59 or within 10 years of menopause) and healthy women
• Individualize therapy
• Progestin is indicated if she has a uterus
• Vaginal therapy for local sxs
• Lowest dose-shortest time
Both estrogen therapy and estrogen with progestin therapy increase the risk of blood clots in the legs and lungs. Lower risk w/ low dose and transdermal

Although the risks of blood clots and strokes increase with either type of HT, the risk is rare in the 50-59 year-old age group

An increased risk in breast cancer is seen in 3-5 years of continuous estrogen/progestin therapy, not ET

The risk decreases after HT is stopped

Compounded HT is not FDA approved
NAMS HT Position Statement 2012

  March 2012 Vol. 19, No. 3, pp. 257/271

- Health Outcomes After Stopping Conjugated Equine Estrogens Among Postmenopausal Women With Prior Hysterectomy A Randomized Controlled Trial Andrea Z. LaCroix, PhD Rowan T. Chlebowski, MD, PhD for the WHI Investigators
  *JAMA. 2011;305(13):1305-1314*
Less but more appropriate HT use since WHI

FIG. 1. Annual prevalence levels of hormone therapy (HT) use from 1998 to 2007.
Indications

- Yes, HT is still indicated for menopausal sxs
- It is the best therapy for this indication
- Prevention of menopausal osteoporosis ("MOP") and fracture without selection for osteoporosis
Individualize Rx

- Use HT for sx (hot flashes, etc)
  - Other therapies may be better for anxiety, sleep, etc

- prevention of MOP and MOP fracture

- Avoid with established risk factors
  - VTE, stroke, CAD, Ca, migraine (w/ aura)

- No uterus: No progestin

- Local symptoms, local therapy
Risks: VTE

- Baseline risk 1-5/10,000
- Obesity triples VTE risk
- Oral HT doubles VTE risk at any BMI
  - OC 4-6x, pregnancy 10+x, post partum 100x
- May be dose dependent.
- Transdermal HT may not > risk
Risks: Stroke

- WHI 2002 found > risk for ischemic, not hemorrhagic
- 10 yrs later, eval by age finds no > risk in perimenopausal aged women
- No > in HERS or WEST (2001), WISDOM (2007)
  - NHS (HT, ET> 0.3mg CE RR 1.58)
CAD

- 2002 WHI found overall > risk
  - MI, plaque formation, carotid intima thickness
- F/u distrib by age finds < risk in perimenopause
- KEEPS trial agrees
  - Kronos Early Estrogen Prevention Study
- HT is not intended for prevention of CAD
Kronos Early Estrogen Prevention Study

- 4yr, 727 women < 3yrs from menopause age 42-59 (mean 52). 64% completed

- 0.45mg CEE po or 0.05mg Climara patch + Prometrium 200mg po qhs x 12/mo vs placebo

- (contrast WHI: 16,000 age 50-79, mean age 63, Prempro 0.625/2.5mg po vs placebo, 50% completed)

- Presented at NAMS 2012 (Menopause.org)
KEEPS

- < Hot flashes, Night sweats
- > BMD
- > sexual lubrication, < dyspareunia
  - > arousal (Climara)
- No change in breast or endometrial ca, TIA, stroke, MI, VTE (too small)
• CE > HDL and < LDL but > TG, CRP
• Climara: no change but < Insulin resistance
• CE < depression and anxiety
• No change in cognition
• Too little coronary artery calcium progression to differentiate between groups but trend to <
Timing:
Age < 60 or < 10 yrs since menopause

- CAD and Alzheimer’s Disease:
  - start young or stay on but don’t start old or restart after too long
  - HT is not indicated for prevention
- HT decreases risk total mortality 30%
- HT < dx of new onset DM2 (HR 0.79)
- Confounded by suggestion of < breast cancer if HT delayed to 5 yrs after menopause
Risks: Breast Cancer

- 8 more cancers/10,000 in WHI EPT 5yrs, E3N, MWS
- ET: 6 fewer with 7 yrs WHI, 13 more in MWS
- type of P may matter
  - Small studies suggest OMP safer
- > risk recurrence w/ survivor HT use
Risks: Endometrial Cancer

- Heralded by bleeding
  - Source of 1-4% of postmenopausal bleeding

- Unopposed ET
  - RR 2.3 overall and 9.5 > 10 yrs

- Adequate progestin use negates risk

- MPA 2.5, NE 0.75mg, P 100mg

- Transdermal P is **NOT** adequate prevention
  - This is the essential reason for P use
Postmenopausal bleeding

- Bleeding > 1 yr from LMP
- Most common reason to stop HT
- Start with pelvic sono
- Consider referral, EMBx
Postmenopausal bleeding

- Well visualized endometrial echo <= 4mm suggests low risk of pathology. No EMBx
- > 4mm, heterogeneous: referral or EMBx
- SIS, hysteroscopy
"Thick endometrium"

- Without bleeding, ? incidental
  - Artifact of imaging
  - Atrophic polyp, Submucous fibroid
  - Anechoic fluid with thin walls (<2mm)

- Consider w/u, esp w/ co-morbidity
  - Heterogeneity, esp w/ doppler
  - Fluid with thick (>2mm) walls
Individualize Therapy

- Vaginal-only therapy for local-only sx's
  - Atrophic vaginitis
  - Atrophy associated dyspareunia
  - Recurrent UTIs, OAB (systemic doesn’t work)
  - Progestin not generally indicated
Vaginal Therapy for local sxs

- Creams: 1/2 gm twice weekly (can load daily for 2-3 weeks)
  - Premarin 0.625mg/gm
  - Estrace 0.01% (100mcg/gm)
    - 14mcg/d
- Vagifem 10mcg (3mcg/d)
  - Twice weekly (after load)
- Estring 2mg q 3 months
  - 7.5mcg/d
## Menopausal Hormone Therapy

<table>
<thead>
<tr>
<th>Name</th>
<th>Hormone(s)</th>
<th>Vehicle</th>
<th>Dosage</th>
<th>Frequency</th>
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<tr>
<td><strong>CONTRACEPTIVE</strong></td>
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<tr>
<td>CORTON&lt;br&gt;synthetic cort, estradiol 1</td>
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<td>0.15mg</td>
<td>0.625mg</td>
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<td>ESTROX&lt;br&gt;synthetic cort, estradiol 1</td>
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<td>ESTRAD(16)&lt;br&gt;estradiol (16mg)</td>
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<td>NOLVAD&lt;br&gt;estradiol</td>
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<td>OESTRUD&lt;br&gt;estradiol</td>
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<tr>
<td>PREMAR&lt;br&gt;estradiol</td>
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<td><strong>HORMONE THERAPY</strong></td>
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</tbody>
</table>

**Side effects and precautions:**

- Oral estrogen can cause nausea, bloating, and fluid retention.
- Transdermal estrogen (patches) can cause skin irritation and breakthrough bleeding.
- Vaginal estrogen can cause vaginal irritation and discharge.

**References:**

- Raszka VR, et al. (2010). Hormone therapy for menopause. The American Journal of Medicine, 123(1 suppl 1A), S1-S6.
Bio Identical Hormones

- Biologically similar to ovarian hormones
- Several FDA approved brands
  - Estrace, generic E2, patches, FemRing, vaginal estrogens
  - Prometrium (OMP)
- Compounding

ESTROGENS

- Estradiol
- Estrone
- Estriol
Bio Identical Hormones

- Compounding Pharmacies
  - Not FDA regulated
    - safety, efficacy, standardization, purity
  - Not standardized for you (P dose)
  - Cost, E3?, sx from rapid absorption
  - Transdermal P NOT indicated for prevention of endometrial hyperplasia

- Not enough data to suggest either E or OMP more safe than CEE or synthetics
Lowest dose/shortest time

- This is a drug, not a fountain of youth
  - HT associated breast cancer risk
- Continue for sx, MOP/fracture prevention
  - Aware of risks/benefits
  - Other therapies not appropriate
Alternatives

- Oral Micronized Progesterone
  - Effective for Rx of hot flashes and night sweats
  - Improved sleep
  - No serious adverse events

- Christine L. Hitchcock, PhD and Jerilynn C. Prior, BA, MD Oral micronized progesterone for vasomotor symptoms - a placebo-controlled randomized trial in healthy postmenopausal women Menopause: 2012 Vol. 19, No. 8, pp. 886/893
• Potential initial withdrawal bleeding
  • Endometrial protection should follow

• E3N: No > breast ca risk w/ E compared to E + MPA

• Does not increase VTE risk

Alternatives

- SSRIs
- Clonidine, Gabapentin
- Black Cohosh (Remifemin)
- Acupuncture, yoga, etc
- Vaginal lubricants, moisturizers


What will be new

- Combination of SERM and estrogen
  - SERM will block adverse E effects
- Polymorphisms
  - Timing of menarche and menopause
  - Hot flashes
  - Osteoporosis, lipids, etc
Estrogen Pathways
Summary - What’s New

- HT is indicated for sxs relief and prevention of osteoporosis.
- Timing is important and Rx individualized
- Local Rx for local sxs
- The progestin matters
- Polymorphisms