Menopause Update

2013

Disclosure of Financial Relationships

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Presentation of a Case

A.R. is a 52 year old woman who presents with complaints of hot flashes, irritability, and diffuse muscle aches after stopping her HT when she heard it causes strokes. However, a friend who lives in San Diego gave her a copy of a “Harvard Women’s Health Watch” that suggests that since she has a high risk of heart disease, she should take HT. The same friend gave her a local newspaper article quoting famous gynecologists who said the same thing. She asks for your advice.
Presentation of a Case

**Allergies:** None

**PMHx/PSHx:** s/p hysterectomy for fibroids, age 40

**Medications:** None

**Social History:** Married, no children. Works as a lawyer. Has smoked one pack per day for 35 years. Does not drink alcohol. No regular exercise. Eats few fruits and vegetables.

**ROS:** Last period age 51. Vaginal dryness uncomfortable during sex.

**BMI= 27 BP= 139/89 HR= 80, reg.RR=12 T= 37 C, remainder of the exam unremarkable, except vaginal atrophy.**

**Labs:** TC 244 mg/dl, LDL 159 mg/dl, HDL 35 mg/dl TG 240 mg/dl, Fasting glucose= 109 mg/dl, Mammogram, Pap smear, Colonoscopy WNL

**Framingham global 10-year risk for cardiac event = 10%**

When you finish examining her, she presents you with a list of additional questions, including:

- I am having trouble with my memory, is it from my menopause?
- My friend has depression, is it because she is in menopause?
- If I don’t take estrogen, will my skin look old?
- Does estrogen cause breast cancer?
- If I take estrogen, is bioidentical safer?

Menopause

New Information on Natural History and Associated Symptoms

Systemic symptoms of menopause are not all associated with the degree of vasomotor symptoms:

- Depression is more common during the menopause transition
- Sleep disturbance occurs in women without vasomotor symptoms
- Cognitive changes reported by some women at the time of menopause relate to the stage of menopause, and improve when the menopause transition is completed

Study of Women’s Health Across the Nation (SWAN):

<table>
<thead>
<tr>
<th>Menopausal Status or Age</th>
<th>Not adjusted for VMS</th>
<th>Adjusted for VMS</th>
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<tbody>
<tr>
<td>Relative Risk of Major Depression</td>
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<tr>
<td>Pre-menopause</td>
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<td>2.5</td>
</tr>
<tr>
<td>Post-menopause</td>
<td>3.5</td>
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</tr>
</tbody>
</table>

*Adjusted for prior major depression, use of psychotropic medications, life events, BMI
*Trend toward decreasing RR more than 2 yrs after menopause

Adapted from: Bromberger Psychological Medicine 2011
Perimenopause is Bad for Your Brain, but You Bounce Back in Postmenopause

Vasomotor symptoms

Hormonal Treatment

Treatment of Menopausal Symptoms: Hormone Therapy

- Hormone therapy remains the most effective treatment for vasomotor symptoms, with a reduction in symptoms of 80-90%.
- Overall risks of hormone therapy are low for otherwise healthy women at the time of menopause.
- For women with a uterus, estrogen without a progestin increases the risk of endometrial cancer, and is not recommended in most cases.
- Both estrogen and estrogen + progestin increased stroke risk in WHI, whether they were started close to menopause or not. Based on this, long term use of hormones for chronic disease prevention is not recommended.

Women’s Health Initiative Estrogen and Progestin
Arm: Absolute Excess Risk

CHD Events: 7/10,000 woman years
Stroke Events: 8/10,000 woman years
Pulmonary Emboli: 8/10,000 woman years
Invasive Breast CA: 8/10,000 woman years

Writing Group for the WHI Investigators JAMA 2002

Estrogen + Progestin
Risk-Benefit Balance 2013

Benefits
- Vasomotor Symptoms
- Vaginal Atrophy
- CHD (when used for 10 yrs at time of menopause)
- Osteoporosis
- Colon Cancer
- Skin Preservation
- Depression

Risks
- Breast Cancer (includes increased breast cancer mortality)
- Total Cancer (follow up studies)
- CHD (when started remote from menopause)
- Stroke
- dementia (women over 65 years)
- Pancreatitis
- GIST
- Gallbladder Disease
- Kidney Stones
- Breast/Bleeding Side Effects
- Ovarian Cancer


Estrogen plus Progestin and Breast Cancer Incidence and Mortality in Postmenopausal Women: Mean Follow up 11 years

Writing Group for the WHI Investigators JAMA 2002

Hazard Ratio

Breast Cancer Mortality Total Mortality after Breast Cancer Diagnosis

+ 95% CI 1.00 - 1.04
++ 95% CI 1.01 - 2.48

Chlebowski JAMA 2010; 304:1684
Estrogen Alone Risk-Benefit Balance 2013

Benefits
- Vasomotor Symptoms (on therapy)
- Vaginal Atrophy (on therapy)
- Breast Cancer Incidence (5-6 yrs of therapy, 10.7 yrs of follow-up)
- MI (age 50-59 years, 5-6 yrs therapy, 10.7 yrs of follow-up)
- Osteoporosis (on therapy)
- Skin Preservation
- Depression

Risks (while on therapy)
- Stroke
- Dementia (women over 65 years)
- DVT/PE
- Endometrial Hyperplasia/Cancer
- Kidney Stones
- Breast/Bleeding Side Effects
- Pancreatitis
- Ovarian Cancer

Postmenopausal Women: Estrogen-Only Menopausal Hormone Therapy in WHI

- Invasive breast cancers in women assigned to CEE were larger (1.8 cm compared to 1.5 cm, p<.03)
- Invasive breast cancers in women assigned to CEE tended to be node positive (36% vs. 23%, p<.07)

Stefanick JAMA 2006

Principles of Hormone Treatment

- Very important to add progestin in women with a uterus
  - In the PEP trial, 34% of women on unopposed estrogen developed advanced hyperplasia after 3 years of treatment

Writing Group for the PEP trial. JAMA 1996

Breast Cancer and Different HT Formulations

"Million Woman Study Shows Breast Cancer Risk"

- Prospective cohort study in Britain
- For CURRENT USERS, increased incidence of breast CA for both E alone (RR = 1.3) and E + P (RR = 2.0)
- Increased for pills, patches, implants, continuous, and sequential regimens

ACOG Committee Opinion Hormone Therapy and Heart Disease. Obstet Gynecol 2000; USPSTF October 2012
"Not only is evidence lacking to support superiority claims of compounded bioidentical hormones over conventional menopausal hormone therapy, but these claims also pose the additional risks of variable purity and potency and lack efficacy and safety data."

- Under and overdosage are of concern, eg. endometrial hyperplasia and cancer are a concern with untested/unreliable doses of estrogen and progestins
- Estradiol and micronized progesterone are available in proven formulations, and are preferred given available data

Source: ACOG Committee Opinion #532, August 2012; FDA 2008

Vasomotor symptoms

Non-Hormonal Treatment

Escitalopram for Hot Flashes in Healthy Menopausal Women: A Randomized Controlled Trial

Mean # of Hot Flashes

*Statistically fewer hot flashes than placebo

Escitalopram Placebo

% indicating better sleep

*p < .001 for each week, improvement in sleep-related daytime functioning p<0.05 for zolpidem group

Back to the Future: Sleep Aids for Hot Flash related sleep problems

Note: FDA recommended 5 mg dose not be exceeded for women

Vasomotor symptoms

Alternative and Complementary Therapies
Common Complementary Treatments for Vasomotor Symptoms Studied in at Least One Randomized, Controlled Trial

- Soy
- Vitamin E
- Black Cohosh
- Oil of Primrose
- "Yam Progesterone"
- Dong Quai
- Red Clover
- Ginseng
- Acupuncture

Binding Affinities for ERα and ERβ

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<thead>
<tr>
<th></th>
<th>ERα</th>
<th>ERβ</th>
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<tr>
<td>Genistein</td>
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<td>Coumestrol</td>
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<tr>
<td>Daidzein</td>
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<td>0.5</td>
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</table>

Complementary Treatments for Vasomotor Symptoms

- Efficacy is similar to placebo
- Placebo benefit is a 25%-50% reduction in vasomotor symptoms


The Placebo Effect and Hot Flashes

- "We feel that some of the dramatic results achieved with preparations such as vitamin E and a famous vegetable compound now on the market must be attributed to the psychological effect of a placebo..."
  - Kupperman, et al, JAMA 1959, as quoted by Nancy King Reame, Menopause 2005

An Intensive Behavioral Weight Loss Intervention and Hot Flushes in Women

- Changes in physical activity, calorie intake, blood pressure, and physical and mental functioning were not associated with a change in hot flush symptoms
Menopause Facts:
- Hot Flashes and Associated Symptoms:
  - 85% experience hot flashes
  - 65% experience night sweats
  - 35% experience associated symptoms

6 Weeks of Weekly Cognitive Behavioral Therapy Improves Quality of Life for Women with Hot Flashes and Night Sweats
- Statistically better mood, sleep, quality of life.
- No significant difference in hot flash frequency

Dysparunia and Sexual Dysfunction

Study of Women's Health Across the Nation
- Infrequent or no sexual desire: 9%
- Content with sexual experiences: 91%

Treatment of vaginal atrophy
- Lubricants
  - E.g., KY Jelly®, Astroglide®, etc., prn or regularly
  - Replens® on a regular basis
- Local hormone therapies: more effective
  - Estradiol® insert q 2 weeks
  - Vagifem® insert 10 mg nightly x 14 days, then biw
  - "Low dose" topical estrgen
- Cochrane review found 7 more risk of endometrial hyperplasia
- Increased risk of endometrial hyperplasia
- Systemic hormone therapy
  - Only indicated if also used for vasomotor symptoms

Treatment of vaginal atrophy
- Ospemifene (Osphea®)
  - SERM approved in 2013 by the FDA for treatment of moderate to severe dyspareunia
  - Boxed warning: risk of endometrial cancer, stroke, MI, DVT, contraindicated in pregnancy, known or suspected estrogen-dependent neoplasia, use of estrogen, another SERM, fluconazole, rifampin
  - 52 week study of endometrial safety showed RR 3 for endometrial thickening and RR 4 for proliferative endometrium; need for progestin if used longer term
  - Studies lacked power to adequately assess stroke and DVT, but increased risk known for HT and other SERMS
  - Breast cancer, osteoporosis effects unknown
  - Dose 60 mg daily with food, based on limited safety data, would possibly consider in refractory cases
Testosterone for Low Libido in Postmenopausal Women Not Taking Estrogen: Mean Scores on Sexual Desire Domain of Profile of Female Sexual Function

- Baseline
- 24 weeks

**1.4 more satisfying sexual encounters/mo p<.001**

Davis NEJM 2008

Conclusions: ACOG Practice Bulletin 2011

- Level A: “Transdermal testosterone has been shown to be effective for the short-term treatment of hypoactive sexual desire disorder, with little evidence to support long term use” (not FDA approved)
- Level B “The main risks associated with androgen replacement... are hirsutism, acne, virilization... cardiovascular complications, [and] a possible association with breast cancer.
- Level C: “There is no proven clinical utility to monitoring androgen levels before or during treatment for hypoactive sexual desire disorder [in women]”

ACOG Obstet Gynecol 2011

Presentation of a Case

- Should I take hormones to prevent heart disease? No, hormones are not indicated for prevention.
- Should I take hormones for menopause symptoms? Maybe, each woman and her provider should decide based on risks and benefits.
- I am having trouble with my memory, is it from my menopause? It could be, and if so, it will get better.
- My friend has depression, is it because she is in menopause? Menopause increases the risk of depression.
- If I don’t take estrogen, will my skin look old? Estrogen therapy doesn’t seem to help much with skin aging, but sun screens do.
- Does estrogen cause breast cancer? Hormone therapy for women with a uterus can cause breast cancer. Use should be limited to shortest duration needed for symptoms. Breast cancer survivors should avoid estrogen, if possible.
- If I take estrogen, is bioidentical safer? There is no evidence that bioidentical is safer, and it can be harmful if “unbalanced”, because too little progesteron can lead to uterine cancer.