GRAND ROUNDS

DEPARTMENT OF OBSTETRICS, GYNECOLOGY & WOMEN’S HEALTH

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“MENOPAUSE UPDATE”

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Objectives

1. Review management and health promotion of the menopausal woman.
2. Review the latest AGOG guidelines/NAMS guidelines for Hormone therapy use; including risks and benefits.
3. Define the various products and delivery formulas available commercially including “bio-identical” hormones.
4. Discuss challenges practitioners face when prescribing hormone therapy.
Practice Model at WHS

- **Foundation in OB/GYN Care**
  - OB/GYN MD 7, Certified Nurse Midwives 7, WHNP DNP 1

- **Primary Care**
  - Family Medicine 3, Internal Medicine 1
  - Pharm D 1
  - Psychologist 1

- **Integrative Care Model**
  - MD/APRNs
  - Acupuncturist
  - Integrative Nutritionist
  - Health Coach
  - Reiki Therapist
Mature Woman’s Health: setting the stage

- **Care focused on ages 40-65**
  - See approximately 300 patients per month in this age group
  - Close to 40% of clinic patients are 40 or older

- **Mid-life Transition**
  - Menopause can be viewed as a sentinel event presenting a unique opportunity to work with health care providers (NAMs 2010)
  - Most report good health at age 65 (agingstats.gov, 2012)

- **What do we see?**
  - Vasomotor symptoms, sleep disturbance, fatigue, vaginal dryness, decreased libido, mood disorders (depression/anxiety), cognitive changes, bone health
• In the past decade fewer than one in four adults age 50-64 received core preventive care.

• 50% of women who get cervical cancer have not been adequately screened, routine mammograms in this age group significantly reduces deaths from breast cancer and screening for colorectal cancer is rated as one of the highest ranked preventive services with the lowest delivery cost.

• ...by the time they reach their sixth decade, 70 percent will have been diagnosed with one or more chronic health conditions – and nearly half will have two or more.

(Promoting Preventive Services for Adults: 40-64 (CDC, AARP, AMA 2009)
THE MID-LIFE FEMALE

- Emerging demographics: In Minnesota, women 50 years and older make up 35% of the female population (MN State Demographic Center 2012)

- Average life expectancy for women is 81+ years (agingstats.gov, 2012)
MENOPAUSE: normal physiological event

• The cessation of menstruation
• 12 months after the LMP
• Average age is 51
• Postmenopause – time following menopause
• Perimenopause — the transition to menopause
• Premature menopause — before or at age 40
MENOPAUSE

• Menopause is a dynamic transitional mid-life experience, not a destination.
• An individualized approach is needed...no two experiences are the same.
• Before prescribing hormone therapy - evaluate each woman's complete medical history and symptoms, an identification of her individual risks and a discussion on evidence based risks and benefits.
LIFESTYLE MODIFICATIONS

Self Management:
  • Regulate core body temperature: *fan, layers of clothing*
  • Identify triggers: *spicy foods, caffeine, alcohol, smoking, etc.*
  • Stress management and relaxation techniques
  • Weight Loss: normal BMI
  • Exercise: manage weight and mood
  • Healthy diet

Supplements and botanicals:

Other systems of healing: i.e. TCM/acupuncture

Mindfulness & Wellbeing: the mature woman course
HORMONE THERAPY USE

• Prior to WHI at least 40% of postmenopausal women used HT.
• Immediately following results from the 2002 study < 4% of women reported use of HT.
• RX for (HT) in the US continues a slow, steady downward trend seen over the last several years.
The Women’s Health Initiative (WHI) was designed to determine the benefits and risks of hormone therapy (HT) for healthy postmenopausal women for chronic disease prevention.

The first large-scale randomized prevention trial to address risks and benefits:

- Enrolled 27,347 postmenopausal women aged 50-70
- Enrolled 1993-1998 at 40 US clinical centers
- Used CEE + MPA (most common formulation at the time)

The intervention phase (CEE + MPA) was stopped on 7/7/2002 due to increased breast cancer risk and an unfavorable risk-to-benefit ratio (after a median of 5.6 years).

The intervention phase (CEE alone) ended on 2/29/2004 after a median of 7.2 years due to increased stroke incidence.

The follow-up phases continued through September 30, 2010.
WHI LIMITATIONS FOR GENERALIZING

• Only one route of administration (oral)
• Only one formulation of estrogen (CEE) and only one formulation of progestogen (MPA)
• Enrolled healthy postmenopausal women aged 50-79 (ave age 63) vs symptomatic, recently postmenopausal women
• Primary outcome was chronic disease prevention not symptomatic benefit
Guidelines for Hormone Therapy Use

- JAMA October 2013
  - Review article on WHI
- NAMS: North American Menopause Society
  - 2012 HT position Statement
- ACOG: American Congress of Obstetricians & Gynecologists
  - Committee Opinion(s)
  - Practice Bulletin No. 141
- Global Consensus Statement on Menopausal HT
Intervention phase with **CEE + MPA:**

- **RISKS:** ↑ CHD: 196 vs. 159;
  
  ↑ Breast Cancer: 206 vs. 155;
  
  ↑ in stroke, PE, dementia, GB dz, urinary incon

- **BENEFITS:** ↓ hip fractures, colon cancer, diabetes & VM sx.

Intervention phase with **CEE alone:**

- Younger women (aged 50-59) had more favorable results
  
  ↓CHD: 204 vs. 222; ↓Breast Cancer 168 vs. 216
  
  (unexpected and differ from observational studies)

**Conclusion**

- Do not the use of HT for chronic disease prevention
- Appropriate for symptoms management in some women
SYMPTOM CONTROL MANAGEMENT

• Vasomotor symptoms (hot flashes & night sweats)
  • Estrogen therapy is the most effective treatment
  • Primary indication for hormone therapy
  • Progesterone alone not as effective
• Vaginal symptoms
  • Estrogen therapy is the most effective treatment
  • If only treating vaginal symptoms: vaginal ET
• Sexual dysfunction
  • HT NOT recommended for sole treatment
SYMPTOM CONTROL MANAGEMENT, CONT

- **Urinary Tract Health**
  - Only ET vaginally has been shown to be effective.
  - No HT product has FDA approval.

- **Quality of Life**
  - HT can results in an improvement in HQOL in symptomatic women.
  - Not FDA approval for QOL.

- **Mood disorders**
  - Insufficient data to use HT as treatment.
  - Progestins may worsen mood.
SYMPTOM CONTROL MANAGEMENT, CONT

• Bone loss/health
  • HT does reduce osteoporotic fractures
  • NOT recommended as primary treatment
  • Premature menopause an exception

• Cognition
  • Lack of data; HT not recommended for prevention or treatment.
  • Cognitive assessment conducted ~ 7.2 years post intervention = neutral results (WHI).
  • Study of Women’s Health Across the Nation, women who initiated HT before their final period vs. women who initiated HT after their final period had a beneficial cognitive effect.
Chronic Disease Risk

Coronary Heart Disease:

• Observational studies vs RCT

• Timing Hypothesis

• Appears to be some CV benefit when used close to the onset of menopause

• Women who initiate HT > 10 years beyond menopause are at increased risk for CHD

• Insufficient data to recommend HT for primary or secondary prevention of coronary heart disease

Obstet Gynecol 2013;121:1407-10 (ACOG #565)
Chronic Disease Risk, cont.

**Stroke:**
- WHI: showed increase risk of ischemic stroke
- Timing of use is important: no↑ risk in women 50-59 years old
- Increase risk dissipates after stopping HT

**Venous Thromboembolism**
- Increase risk with oral HT in all women
  - A 2-5 fold risk is cited for HT users
  - Preexisting risk factors increase risk
- Transdermal ET has possible thrombosis-sparing properties
  (Canonico, Circulation 2007)
- Lower dose may have less VTE risk
  (Obstet Gynecol 2013;121:887-90 (ACOG #556))
Breast Cancer Risk

- Dx of breast cancer increases with EPT use beyond 3-5 years:
  - BC: 8/10,000 (beyond 3-5 years)
  - EPT increases mammographic density
  - Increased mortality: 2 additional deaths/10,000/yr
  - Lower risk of breast cancer with “timing hypothesis”
  - Absolute risk is still lower in younger women

- Estrogen therapy alone, per WHI:
  - No increased risk after 7 years of use
    - Observed in all 3 age groups
  - Findings were not observed in Million Women Study

Menopause Vol 19, No. 32012
## Summary of Outcome

### Risks & Benefits of HT

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Vasomotor symptom relief</td>
<td>• Possible increase in CHD*</td>
</tr>
<tr>
<td>• Vaginal/vulvar atrophy relief</td>
<td>• ↑ risk of ischemic stroke*</td>
</tr>
<tr>
<td>• Improves QOL in symptomatic women</td>
<td>• ↑ risk of VTE</td>
</tr>
<tr>
<td>• Decrease in postmenopausal osteoporotic fractures</td>
<td>• ↑ Breast cancer *</td>
</tr>
<tr>
<td>• Possible decrease in CHD &amp; coronary artery calcium (ET)*</td>
<td>• ↑ endometrial cancer with unopposed ET</td>
</tr>
<tr>
<td></td>
<td>• ↑ ovarian cancer &gt; 10 years</td>
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*varies with timing of use
Key to HT Discussion

• Individualization:
  • Health history → personal risk factors and family hx
  • Beliefs and fears
  • Quality of life priorities
• Absolute risk is low for women ages 50-59
• If uterus present: systemic HT must include a progesterone/progestin (EPT) to prevent endometrial hyperplasia.
49-year-old P2012 woman presents with complaints of hot flashes, night sweats, poor sleep, irregular menses and painful intercourse. Symptoms interfere with her QOL.

Ob/gynHx: NSVD x2, h/o CIN I, no h/o STIs, sexually active in monogamous relationship, using BTL for contraception

PMHx: anxiety

PSurgHx: laparoscopic bilateral tubal ligation

Meds: Celexa, Vitamin D

Family Hx: maternal grandmother had breast cancer in her 70s, maternal grandfather h/o colon cancer
Evaluation, Discussion & Treatment Options

PE: might include EMB to evaluate menstrual irregularity

LABS: +/-
  • Estradiol/FSH
  • Thyroid levels (TSH, FT3, FT4)
  • Vitamin D level

Treatment options:
  • Systemic HT: both estrogen and progestin
    • (cyclic vs continuous)
    • Premarin .625 mg and MPA 2.5 mg
    • Estradiol 1 mg and MPA 2.5 mg
    • Estradiol 1 mg and progesterone
    • Transdermal estradiol and progesterone.
<table>
<thead>
<tr>
<th>COMMERCIALLY AVAILABLE HORMONE REPLACEMENT PRODUCTS</th>
<th>Products</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Estrogen only</strong></td>
<td>Conjugated equine estrogen (CEE) Synthetic conjugated estrogen Esterified estrogen Estradiol Estropipate</td>
<td>Oral tablets</td>
</tr>
<tr>
<td><strong>Oral Progesterone only</strong></td>
<td>Medroxyprogesterone acetate (MPA) Micronized progesterone</td>
<td>Oral tablet, capsules</td>
</tr>
<tr>
<td><strong>Transdermal Estrogen</strong></td>
<td>Estradiol</td>
<td>Patch, gel, emulsion, spray</td>
</tr>
<tr>
<td><strong>Vaginal Estrogen</strong></td>
<td>Conjugated equine estrogen Estradiol</td>
<td>Vaginal cream, ring, tablet</td>
</tr>
<tr>
<td><strong>Combination Estrogen and Progestin</strong></td>
<td>CEE + MPA Estradiol + norethindrone Estradiol + drospirenone Estradiol + norgestimate Estradiol + levonorgestrel</td>
<td>Oral tablets Transdermal patches</td>
</tr>
</tbody>
</table>
Case Study #1: Follow-up

TX: Systemic HT: Estradiol .5 mg and progesterone 100 mg

six months later: Hot flashes resolved, sleeping well but vaginal dryness/dyspareunia persist

Options:

• Increase estradiol to 1 mg daily

• Add vaginal estrogen
  
  • Vaginal ring (17-beta estradiol, estradiol acetate) [estring]
  
  • Vaginal tablets (estradiol hemihydrate) [vagifem]
  
  • Vaginal creams (17-beta estradiol, conjugated equine estrogens) [estrace or premarin]
CASE STUDY #2

• **52 year, G0 with LMP** ~ one year ago. Continues with frequent hot flashes, night sweats, moodiness, irritability, insomnia, and decreased libido

• “My hormones are out of balance and I can’t take it any more! I have read about bio-identical hormones and think that might be helpful and safer... I won’t take that “pregnant mares urine.”

• **PMH:** GAD, IBS, hyperlipidemia, multiple drug and chemical sensitivities
BIOIDENTICAL HORMONES

- Plant-derived hormones that are chemically similar and structurally identical to those produced by the body.
- Bioidentical hormones include commercially available products approved by the FDA, such as micronized progesterone and estradiol.
  - No evidence to suggest greater safety or superiority.
  - Compounded HT from pharmacies that formulate an individual prescription may be an option for women with sensitivities/intolerances.
  - Transition women from comp'd – commercially available
TREATMENT OPTIONS

1) Discussion on HT: risks/benefits that are attributed to all HT products.

2) Provide options:
FDA approved bio-identical HT
• Estradiol patch (.0375 - .05) and micronized progesterone
  • (avoids first pass, decreased VTE, improves insulin resistance and multiple dosing)
• Estradiol jel/sprays (.5-.1 mg) and Progesterone
• Oral estradiol (.5-1- mg) and micronized progesterone

Other conventional non-bio-identical
• Premarin .45 - .625 mg and Medroxyprogesterone 2.5 mg

Compounded product
• Estradiol hypoallergenic cream and micronized progesterone

3) Follow-up and anticipate an adjustment period
HT Options

Bioidentical

Compounded

Estrogens
- Estrone, Estradiol, Estriol
  - Transdermal, Oral or Vaginal

Progestrone
- Transdermal, Oral

Pharmaceutical Manufactured

Estrogens
- 17-Beta estradiol
  - Transdermal, Oral or Vaginal

Progesterone
- Micronized Progesterone (Prometrium)
  - Oral, Vaginal

Pharmaceutical Manufactured

Estrogens
- Conjugated estrogen, esterified estrogen
  - Oral, Vaginal

Progesterone
- Medroxyprogesterone acetate
  - Oral

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Factors that influence the choice of HT

- Practitioner comfort, knowledge and experience
- Insurance coverage
- Expense
- Medical History
- Ease of use
- Media influences
- Patient request & desire
- Time to discuss Pros/Cons of HT
- Reality of clinical practice
Case Study #3:

65 year-old P3013 woman who presents requesting a refill on HT. Has been on HT since age 50. Has attempted to go off in the past but had severe hot flashes and night sweats. Wants to continue with HT for symptom control and QOL.

Ob/gynHx: NSVD x3, sexually active in monogamous relationship.

PMHx: Hypertension on HCTZ 25 mg

PSurgHx: tubal ligation & Lap Chole

MED: HCTZ 25, Estradiol 1 mg, Provera 2.5 mg

FMHx: sister with breast cancer age 70

HCM: Yearly mammogram
ACOG’s Practice Bulletin:  No. 141: Management of Menopausal Symptoms:  

- Because some women aged 65 years and older may continue to need systemic HT for the management of vasomotor symptoms, ACOG recommends against routine discontinuation of systemic estrogen at age 65 years (vs routine recommending).

NAMS 2012 Position Statement:  

- Optimal duration of therapy differs for EPT and ET - limited by the increased risk of breast cancer after 3-5 years (EPT) and 7 years (ET) found in the WHI. Breast cancer risk increased with duration of current E+P use without evidence for a plateau in the NHS.

- Provided that the woman is well aware of the potential benefits and risk and has clinical supervision (mammogram/HCM), extending HT use with the lowest effective dose is acceptable.
NON-HORMONAL PHARMACEUTICAL

• Historically: Bellergal, Clonidine, methyldopa
• Newer Medications:
  • SNRI: specifically Venlafaxine at 37.5 - 75 mg
  • SSRI: Citalopram 10-20 mg
  • Paroxetine and fluoxetine: avoid if on Tamoxifen—may inhibit the CYP2D6 enzyme resulting in lower levels of endoxifen
  • Only paroxetine 7.5 mg (Brisdelle) is FDA for VM sx
  • Gabapentin: 900 mg at HS reduced hot flashes by 45-66%.

(Pachman, Int J Womens Health. 2010)
On the Horizon

Two new FDA approved drugs for menopausal management:

• Bazedoxifene [Duavee] instead of progestin with conjugated estrogen for hot flushes and osteoporosis prevention

• Ospemifene [Osphena] for vaginal dryness/dyspareunia (oral)

Research will continue to bring valuable information to help women with their decision about HT.
• Constructing an individual benefit-risk profile is essential for every woman considering any HT regimen.
• There is a growing body of evidence that HT formulation, route of administration and the timing of therapy produces different effects.
• The absolute risks known to date for use of HT in healthy women ages 50-59 years are low.
• In contrast, long-term HT or HT initiation in older women is associated with greater risks. (VTE, stroke & breast cancer)
• Use the lowest effective dose – prescribed for the shortest period of time.
THANK YOU
REFERENCES


REFERENCES

Comprehensive meta analysis of 17 studies of soy isoflavone use with > 1200 women:

- Women with >10 hot flashes had a 20.6% reduction of hot flashes & reduced hot flash severity by 26.2%
- 54 mg of soy isoflavones for six weeks to 12 months.
- 7 oz of tofu or 2 glasses soy milk = 50 mg or supplements with at least 19 mg of genistein—a kind of isoflavone

Menopausal women in the US are more than eight times likely to have hot flashes than women in Asian countries.

(Taku, Menopause. 2012)
• The evidence from RCT’s do not consistently demonstrate an effect on menopausal symptoms.

• A beneficial effect of black cohosh on peri-menopausal women cannot be excluded. (Borrelli, *Pharmacology Res*, 2008)

• Anecdotal evidence

Cimicifuga racemosa, a member of the buttercup family a plant native to North America
St. John's Wort is a well-known treatment for mild depression.
May also have a special benefit for women during menopause.
There's some evidence, particularly when combined with black cohosh, that St. John's Wort can improve mood swings associated with menopause.

(Briese, Maturitas. 2007)
RESOURCES: BOTANICALS AND SUPPLEMENTS

- The American Herbal Products Association (AHPA)  
- National Center for Complementary and Alternative Medicine (NCCAM)  
  http://nccam.nih.gov/health/herbsataglance.htm
- National Institute for Health (NIH)  
- Natural Medicine Comprehensive Database:  
  http://naturaldatabase.therapeuticresearch.com/nd/reviews.aspx
Level A ("good or consistent scientific evidence"):

- Systemic HT, with just estrogen or estrogen plus progestin, is the most effective approach for treating vasomotor symptoms.
- Low-dose and ultra-low systemic doses of estrogen have a more favorable adverse effect profile than standard doses.
- Healthcare providers should individualize care and use the lowest effective dose for the shortest duration.
- Thromboembolic disease and breast cancer are risks for combined systemic HT.
- Selective serotonin reuptake inhibitors, selective serotonin and norepinephrine reuptake inhibitors, clonidine, and gabapentin relieve vasomotor symptoms and are alternatives to HT.
- Local estrogen therapy is advised for isolated atrophic vaginal symptoms.

Level B conclusions ("limited or inconsistent scientific evidence"):

- Data do not support use of progestin alone, testosterone, compounded bioidentical hormones, phytoestrogens, herbal supplements, and lifestyle modifications.
- "Common sense lifestyle solutions" are layering clothing, lowering room temperature, and consuming cool drinks.
- Nonestrogen water-based or silicone-based lubricants and moisturizers may alleviate pain.

Level C recommendation ("based primarily on consensus and expert opinion"):

- Individualize the decision to continue HT.
Effects of the levonorgestrel-releasing intrauterine system plus estrogen therapy in perimenopausal and postmenopausal women: systematic review and meta-analysis.

- Six trials with a total of 518 participants were included. The methodological limitation was an attrition bias. In perimenopausal and postmenopausal women taking ET, the incidence of a proliferative endometrium was comparable between the use of systemic progestogen and LNG-IUS, except for sequential medroxyprogesterone acetate, which had a higher incidence of proliferative endometrium. Descriptive data synthesis showed that ET combined with either LNG-IUS or systemic progestogen effectively relieved climacteric symptoms. Vaginal bleeding and spotting were common in the LNG-IUS group for the first 3 to 6 months of use. The discontinuation rate was not different. There was insufficient evidence to draw any conclusions about the other outcomes.

- **CONCLUSIONS:**

- The LNG-IUS was more effective than sequential medroxyprogesterone acetate but was comparable with other systemic progestogen regimens for endometrial protection in perimenopausal and postmenopausal women taking ET.