Comprehensive Menopause Management: An Update on Current Strategies

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Disclosures
Hologic
Speaker’s Bureau
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Objectives
At the end of this lecture, the attendee will:
1. List two common menopausal symptoms women experience
2. List one difference in oral versus transdermal estrogen therapy from the KEEPS trial
3. Discuss the current risks and benefits of hormone therapy for women in the early post menopause
4. Discuss treatment options for vasomotor symptoms including oral and transdermal estrogen

An Historical Perspective on Hormone Therapy
From where have we come?

Hormone Therapy: Historical Perspective
> 1920’s: Estrogen isolated from the urine of pregnant women and made available
> 1940’s: Ayerst, a Canadian drug maker found a way to make it from pregnant mares and called it “Premarin”
> 1950’s: Massive campaign to promote Premarin as a rejuvenating agent and mood stabilizer for postmenopausal women
  – Premarin ads frequent in medical journals

Hormone Therapy: Historical Perspective
> Mid 1960’s: Approximately 12% of postmenopausal women were taking estrogen
> 1975: New England Journal of Medicine published 2 studies showing that women taking estrogen had as much as 14 times the risk of endometrial cancer as women not on the drug
> Progestogen was added when women had a uterus
> 1992: Premarin was the most widely prescribed drug
Hormone Therapy: Historical Perspective

> 1995: Interest in long term effects
> Most studies were observational
  - Nurses’ Health Study
    - Suggested that estrogen prevented heart disease
    - Reduced the risk of osteoporosis and colon cancer
  - First randomized trial
    - Postmenopausal Estrogen/Progestin Intervention Trial
      - Some cardio-protective findings, but not long enough to see if there were less stroke, MI, or clot

1998: Heart and Estrogen/Progestin Replacement study
- Found that women who already had heart disease did not have prevention of MI’s

Women’s Health Initiative (WHI)
- Designed to answer the question of long term hormone therapy and prevention of heart disease
- 2002: Prempro arm stopped early

The Study That Changed Everything!
What Have We Learned in more than 10 Years?!

1998 and 2002: Results from 2 large randomized controlled trials:
> The Heart and Estrogen/Progestin Replacement Study (HERS): a secondary prevention study
> The Women’s Health Initiative (WHI): a primary prevention study

Changed the widely accepted belief that hormone therapy was protective against cardiovascular disease!

Panic ensued…

> Increased risk of breast cancer
> Increased risk of cardiovascular disease (CHD)
> Increased risk of stroke
> Increased risk of pulmonary embolism (PE)

Change in Practice

> Women stopped taking hormone therapy
> Practitioners stopped prescribing hormone therapy
> Women who wanted hormone therapy couldn’t always get prescriptions
> Confusion increased further with the marketing of so called, “safer” and “bioidentical” products in the marketplace

It’s Time to Rethink, Reboot and Review: Hormone Therapy
Advocacy for women to live with quality
Different Approaches: Individualization of Care

Disclaimer: Presenting an approach that supports evidence-based practice and position statements for practice:

“One goal of The North American Menopause Society (NAMS) is to develop position statements and other reports about clinical issues pertinent to women at midlife and beyond.”

Perimenopause

> The time around the FMP, also called “the menopause transition”
> Begins with variation in the menstrual cycle length
> Associated with a rise in follicle-stimulating hormone (FSH) and ends 1 year after the FMP
> Often the most symptomatic phase for women

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What is menopause?

> Menopause is a normal, natural event, defined as the final menstrual period (FMP), confirmed after 1 year of no menstrual bleeding
> Represents the permanent cessation of menses resulting from loss of ovarian follicular function, usually due to aging

When is menopause?

> Naturally (spontaneously) average age 51
> Prematurely from medical intervention (eg, bilateral oophorectomy, chemotherapy, radiation)
> At any time from impaired ovarian function
> Premature menopause occurs before age 40

Standardization of Stages of Menopause

Stages of Reproductive Aging Workshop (STRAW)
Stages of reproductive aging

> In 2001, the Stages of Reproductive Aging Workshop (STRAW) established a nomenclature for reproductive aging
> In 2011, STRAW+10 updated and modified the model

Menopausal symptoms & signs

**Classic symptoms:**
> Change in menstrual cycle pattern (during perimenopause)
> Vasomotor symptoms (hot flashes & night sweats)
> Vulvovaginal symptoms, dyspareunia
> Sleep disturbances

**Other symptoms sometimes associated with menopause:**
> Cognitive concerns (memory, concentration)
> Psychological symptoms (depression, anxiety, moodiness)
> There is no one universal menopausal syndrome

What About KEEPS?

What recent data has continued to change practice?

Kronos Early Estrogen Prevention Study (KEEPS)

Effects of Oral Conjugated Estrogens vs. Transdermal Estradiol on Common Carotid Artery Intima Media Thickness (CIMT) and Coronary Artery Calcium (CAC)

First data reported: October 3rd, 2012

KEEPS

4-year randomized, double-blinded, placebo-controlled clinical trial of low-dose oral or transdermal estrogen and cyclic monthly progesterone
> Inclusion
  - Healthy women ages 42 to 59 (mean age 52)
  - Within 3 years after menopause
> Excluded women with evidence of cardiovascular disease
Key Goal of KEEPS

> To compare two formulations of hormones
  – Low dose oral conjugated estrogens
  – Transdermal estradiol
  – Both with cyclical micronized progesterone
> Both studied over 4 years in relationship to:
  – Atherosclerosis progression by noninvasive imaging
  – Carotid intima-media thickness
  – Coronary artery calcium

Main Differences in KEEPS From WHI

> WHI:
  – Mean age 65
  – More than 12 years past the onset of menopause
> KEEPS
  – Average age 52
  – Within 3 years of final menstrual period
> Doses, formulations and routes of delivery of hormones were different
> KEEPS trial much smaller with 727 women enrolled

What Are Some Concerns About WHI?

> WHI did change the approach of recommending hormone therapy as a prevention of cardiovascular disease for older women... BUT...
> The results were often extrapolated to newly menopausal women who were considering hormone therapy for distressing symptoms

Key Findings of KEEPS

> Favorable effects of estrogen in newly menopausal women
  – Reduction in vasomotor symptoms
  – Improvement in several parameters of sexual function
  – Improvement in bone mineral density
  – Oral estrogen: improvement in mood outcomes with decrease in depressive symptoms, anxiety and tension
> No significant increase in adverse events!

Key Differences Between Oral and Transdermal Therapy

> Oral
  – Benefits for mood, depressive symptoms, anxiety and tension
  – LDL lowering and HDL increase
  – Subset of women with low cardiovascular risk
    • Cognitive benefit in terms of memory and verbal learning
> Transdermal
  – Greater reduction in libido-related aspects of sexual function

Applying KEEPS to Practice

> Benefit/Risk analysis
  – Younger women may NOW consider treating their symptoms with knowledge that the risks are different than for women who are in their 60’s, 70’s or 80’s
  – Younger women, in early menopause are also more likely to have the hot flushes, night sweats and other symptoms that can reduce their quality of life
What is an Example of Individualization?

55 year old obese woman with metabolic syndrome.
> May benefit from transdermal estrogen
  – Will not increase her triglycerides or C-reactive protein
  – May improve her insulin resistance
  – May increase libido
> 55 year old with a mild elevation of LDL and low HDL and some mood issues
  – May benefit from oral estrogen
  – If in good cardiovascular health generally
    • May also get additional cognitive benefit in terms of memory and verbal learning

Frequency

> As many as 75% of perimenopausal women in US report hot flashes
> Number of episodes vary
> Few to multiple episodes daily
> Highest occurrence during perimenopause and first 2 years of postmenopause

Treatment of hot flashes

> Treatment based on symptom severity, a woman’s risk factors, and her personal preferences
> Serum estrogen levels are not predictive of hot flash frequency or severity
> Many government-approved formulations of HT
> Off-label use of various non hormonal prescription therapies and various dietary supplements and complementary and alternative options

Cognitive changes

> There is evidence that psychomotor speed and to a lesser extent verbal memory can decline slightly in perimenopause
> Although depression and anxiety are related to cognitive decline, neither mood nor age account for these cognitive changes experienced by some women
> Any transient issue with cognition appears to resolve after menopause

Vulvovaginal symptoms

> Symptoms such as vaginal dryness, vulvovaginal irritation/itching, and dyspareunia are experienced by ~10%-40% of postmenopausal women
> Unlike vasomotor symptoms, which abate over time, vaginal atrophy can be progressive and is unlikely to resolve on its own
> Treatments include: regular sexual activity, lubricants and moisturizers, and local vaginal estrogen

Hormonal Management of Perimenopause

Oral Contraceptive
> Treat menorrhagia
> Treat anovulatory bleeding
> Contraception
> Prevention of bone loss
> Treat vasomotor symptoms
> Increase DVT/PE
Transition Off Hormonal Contraception or to HRT

> Should be done as soon as is appropriate
> Consider a woman's need for contraception when making this transition
> Timing of discontinuation or switch is often difficult
>  – Cessation of menses is not observed

BEWARE THE SPORADIC OVULATION OF THE PERIMENOPAUSAL WOMAN!

Transition Off Hormonal Contraception or to HRT

> Some clinicians choose age 51: median age of menopause
> Some choose 53 to cover those women who reach menopause later than the average age
> Measure of FSH
>  – Off hormonal contraception for 2 weeks prior to measurement, with non-hormonal contraception
>  – If FSH level is consistently above 30mIU/mL, menopausal and transition can be safely made
>  – Hormonal method may be held, with non-hormonal contraception and observation for menses

Menopause Management

> There is no indication for hormone measurements for determining management
> Management is based on severity of symptoms
> Hormone therapy decisions are not based on levels of hormones from any measurement such as saliva testing
> There is no benefit in using potions and lotions of non FDA approved products!
> KEEPS addresses some differences in oral versus transdermal therapy

Bioidentical hormones

> Many well-tested, government-approved HT products contain bioidentical hormones
> Usually refers to compounded formulations
> Compounded HT not tested for efficacy, safety, batch standardization, or purity
> Some compounders make unsubstantiated claims about safety and effectiveness

American College of Obstetricians and Gynecologists (ACOG)

> Because such preparations have not been rigorously tested, only FDA-approved HT formulations are recommended.

ACOG Practice Bulletin 141

NAMS Menopause 2012;19:207-71

NAMS Practice Pearl

What Are the Concerns About Custom-Compounded "Bioidentical" Hormone Therapy?

Harkema AV, Wakefield R, NAMS, Menopause. 2014

(University of Virginia Multi-Studies Center, Charlottesville, VA)

Unsubstantiated claims, lack of scientific safety and efficacy data, and lack of quality assured hormone preparations are the main concerns with "bioidentical" hormone therapy. Although "bioidentical" hormone therapy may provide some relief and help with symptoms, this therapy is not without risk and has not been rigorously tested or validated. Therefore, FDA-approved HT formulations are recommended. (NAMS Menopause 2012;19:207-71)
A Decade After The Women’s Health Initiative—The Experts Do Agree

This 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)

*Report of the study follows in blue

Why now?

> July 9, 2002, the first report from the Women’s Health Initiative (WHI)—the largest and longest trial of postmenopausal women using hormone therapy (HT)
> Debate ensued with the one consistent theme: “Even the experts don’t agree”
> This statement of agreement on the use of HT for symptomatic menopausal women was published on the 10-year anniversary of the first report from the WHI

By whom?

> This solidarity statement was prepared by The North American Menopause Society, the American Society for Reproductive Medicine, and The Endocrine Society
> 12 other leading organizations in women’s health endorsed the statement

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

Five Major Points of Agreement

> 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
> Individualization is key in the decision to use HT
Women With Vaginal Symptoms Only

> The preferred treatments are low doses of vaginal estrogen

Women with a uterus

> Women who still have a uterus need to take a progestogen (progesterone or a similar product) along with the estrogen to prevent cancer of the uterus
> Women who have had their uterus removed can take estrogen alone

Risk of blood clots/stroke

> Both estrogen therapy and estrogen with progestogen therapy increase the risk of blood clots in the legs and lungs
> 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

Risk of breast cancer

> An increased risk in breast cancer is seen in 3-5 years of continuous estrogen/progestogen therapy
> The risk decreases after HT is stopped

Estrogen Therapy

Estrogen/Progestogen Therapy

Primary indication for ET/EPT is to treat moderate to severe menopause symptoms (vasomotor)

> When symptoms are controlled or cease, may be continued though risks and benefits must be weighed
> Approved for prevention but not treatment of osteoporosis
> NAMS and ACOG recommend use of ET/EPT at the lowest effective dose for the shortest time period consistent with treatment goals

Practical Pearls for Prescribing HT

> Route of estrogen impacts risk of thromboembolic events, though data is not extensive
  > Oral estrogen has a first pass through the liver
    • May increase the risk of blood clot compared to transdermal
  > Transdermal estradiol had a 30% lower incidence of VTE than those who took oral estrogen only in a study reported in 2011.
Practical Pearls for Prescribing HT

> Oral estrogen
  - Increases triglycerides by 15%
  - Increases HDL by 10%
  - Decreases LDL by 10%  

LaRosa JC. Metabolic effects of estrogens and progestins. Fertil Steril. 1994; 62(6, suppl):140S-6S.

Practical Pearls for Prescribing Vaginal Therapy

> Vaginal estrogen: Cream, ring and tablet
  - Cream may be less expensive
  - Ring is convenient and left in for 3 months before changing
  - Tablet is convenient and less messy
> Opposition of vaginal estrogen by progestin is not required

Practical Pearls for Prescribing HT

> If transdermal is used for hormone therapy, oral progesterone may be used at HS
> Combination estrogen/progestin patch available
> Start low and increase dose as necessary???
> Start average dose and decrease as symptoms come under control???
> Two products= two copays!!
> Generic products for transdermal patch, oral estrogen and combined estrogen/progestin

Treatment for Dyspareunia

Oral ospemifene 60mg
> FDA approved for the treatment of dyspareunia associated with vulvovaginal atrophy
> Estrogen agonist/antagonist (SERM)
> NAMS

The estrogen agonist/antagonist ospemifene is an oral agent for the treatment of moderate to severe dyspareunia due to GSM/VVA. (Level I)

(In Level I based on good and consistent scientific evidence).

Intrarosa (Prasterone)

Vaginal DHEA for moderate to severe dyspareunia
> FDA approved 11/16
> Once daily vaginal insert
> Two 12 week trials showed reduction in the severity of pain during sexual intercourse compared to placebo
> Most common adverse reactions were vaginal discharge and abnormal Pap tests
> The product was not studied in women with breast cancer

Intrarosa (package insert). Quebec City, Quebec, Canada: Endocutics Inc, 2016.
**Intrarosa (Prasterone)**

- Converted into estrogen and androgen locally
- Contraindicated:
  - Undiagnosed vaginal bleeding
  - History of breast cancer
- Administration
  - Administer 1 insert daily at bedtime intravaginally
  - Use applicator provided; each applicator is for one-time use only
  - Instruct patient to empty bladder and wash hands before handling the vaginal insert and applicator

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**Fractional Laser Treatment for Vulvovaginal Atrophy**

The North American Menopause Society (NAMS) and the American Congress of Obstetricians and Gynecologists (ACOG) agree:

- Further research is needed before this procedure can be recommended for treatment of VVA
- Although the technology is marketed as being FDA approved for broad indications, it is not cleared by the FDA for the specific indication of treating VVA.

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**Dosage of Hormone Therapy**

**Standard Dose**
- Conjugated estrogen 0.625mg/d
- Micronized estradiol-17 Beta 1 mg/d
- Transdermal estradiol-17 Beta 0.0375-0.05

**Low Dose**
- Conjugated estrogen 0.3-0.45mg/d
- Micronized estrogen-17Beta 0.5mg/d
- Transdermal estradiol-17Beta 0.025mg/d

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**Dosage of Hormone Therapy**

**Ultra-Low Dose**
- Micronized estradiol-17Beta 0.25mg/d
- Transdermal estradiol-17Beta 0.014mg/d

**Estrogen combined with estrogen agonist/antagonist**
- Conjugated estrogen 0.45mg/d and bazedoxifene 20mg/d

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**Dosage of Hormone Therapy**

**Systemic HT**, with estrogen alone or in combination with progestin, is the most effective therapy for vasomotor symptoms

**Low-dose and ultra-low dose systemic doses of estrogen** are associated with a better adverse effect profile than standard dose and may reduce vasomotor symptoms in some women

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*Practice Bulletin, No 141, January 2014, The American College of Obstetricians and Gynecologists*
Duration of Use

> Some experts recommend keeping duration of treatment short
> For many women vasomotor symptoms are a long term concern
> Penn Ovarian Aging Study
  – Median duration of moderate to severe VMS was more than 10 years
> For many women, short-term use (3-5 years) will not be sufficient to control symptoms


Duration of use

> With EPT, increased risk of breast cancer incidence and mortality with 3-5 years of use
> With ET, no increase of breast cancer with early postmenopausal use; a decrease was found after hiatus in estrogen exposure
> With ET, potential CAD and CHD benefits with early use
> Initial increase in CHD risk when EPT is initiated further from menopause

NAMS Menopause 2012;19:257-71

Duration of Hormone Therapy Use
NAMS 2012 Position Statement

“...extending EPT use with the lowest effective dose is acceptable under some circumstances, including for the woman who has determined that the benefits of menopause symptom relief outweighs risks, notably after failing an attempt to stop EPT”.

NAMS. Menopause 2012

Use of HT to Treat Menopausal Symptoms: ACOG Guidance

“...ACOG recommends against routine discontinuation of systemic estrogen at age 65 years. As with younger women, use of HT and estrogen therapy should be individualized based on each woman’s risk-benefit ratio and clinical presentation.”


Continuation of Hormone Therapy

> Requires individualized assessment of HT benefits and risks
> Shared decision making
**Discontinuation of Systemic Therapy**

- VMS may recur in as many as 50% of women
- Does not appear to vary between abrupt and tapered discontinuation
- Women may be reluctant to reduce their dose or to stop therapy
- Recommend a 3 month trial off with the understanding that therapy could be restarted

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**Age and Hormone Therapy**

Is 65 too old to continue??

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**American College of Obstetricians and Gynecologists (ACOG)**

Because some women aged ≥65 might still need systemic HT for VMS, HT should not be routinely discontinued at age 65, but, as in younger women, should be individualized.

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**HT summary**

- HT formulation, route of administration, and timing of initiation produce different effects
- Individual benefit-risk profiles are essential
- Absolute risks in healthy women ages 50-59 are low
- Long-term use or HT initiation in older women, however, has greater risks
- Breast cancer risk increases with EPT beyond 3-5 years
- ET can be considered for longer duration of use due to its more favorable safety profile

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**Nonhormonal prescription options**

- Nonhormonal prescription drugs (off-label use):
  - Antidepressant
    - SSRIs: fluoxetine, paroxetine, escitalopram
    - SNRIs: venlafaxine and desvenlafaxine
  - Hypnotic
  - Eszopiclone
  - Anticonvulsant
  - Gabapentin
  - Antihypertensive
  - Clonidine
  - Neuropathic pain drug
  - Pregabalin

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**References**

- **Discontinuation of Systemic Therapy**
  - Kaunitz, A. When should a menopausal woman discontinue hormone therapy. OBG Management, Vol 26;14:59-65.

- **Age and Hormone Therapy**
  - NAMS Statement and Editorial on Increasing Systemic Hormone Therapy After Age 65
  - ACOG Practice Bulletin 141

- **HT summary**
  - Menopause
  - 2012;19:257-71

- **Nonhormonal prescription options**
  - Thacker HL. J Womens Health 2011;20:1007-16
Antidepressants for hot flashes

- Selective serotonin reuptake inhibitors (SSRIs)
  - Fluoxetine
  - Paroxetine
  - Escitalopram
- Serotonin–norepinephrine reuptake inhibitors (SNRIs)
  - Venlafaxine
  - Desvenlafaxine

None of the above are government approved for hot flashes, so use would be considered off-label

Thacker HL. J Womens Health. 2011;20:1007-16

FDA Approved Non-Hormonal Treatment

- Paroxetine 7.5 mg capsule
  - Low dose SSRI
  - Indication: Used to treat moderate to severe hot flashes of menopause
  - Most common side effects
    - Headache, nausea, vomiting

Non-Hormonal, Non-Estrogenic Supplement

Relizen
- Swedish flower pollen extract product
- Randomized, double-blind, placebo controlled trials show significant reduction in hot flashes and improved “quality of life” parameters
- No estrogenic effects
- Does not show inhibition of the CYP2D6 enzyme which is necessary for tamoxifen metabolism

Winther K, Rein E, Hedman C, a herbal remedy made from pollen extracts. Climacteric. 2005;8:162-70
Hellstrom A, Muntzing J, The pollen extract Femal—a nonestrogenic alternative to hormone therapy in women with menopausal symptoms. Menopause. 2007;14:825-829
Goldstein SR, Espie MA, Druckmann R. Does Relizen, a non-hormonal treatment for vasomotor symptoms, inhibit the CYP2D6 enzyme system? Abstract, Menopause, 12/2014

Menopause Management

- Hormone therapy appears to have favorable effects on symptom management and quality of life in newly menopausal women
- Individualization of care is important
- There may be some advantages of transdermal therapy for some women and advantages of oral therapy for others
- Clinical decisions should be based on:
  - The woman’s symptoms
  - Underlying risk factors
  - Personal preferences
  - Priorities for treatment

Conclusion: NAMS 2016 HT Position Statement

“Decisions about duration of HT require individualization, including consideration of personal preferences, balancing potential ongoing benefits and risks, and decisions to continue HT for preventative and/or quality of life purposes”

Shared decision making helps our patients make sound choices

NAMS. 2016. Kanutz AM. Menopause June 2014