MORE THAN JUST HOT FLASHES: ADDRESSING THE OTHER SYMPTOMS OF MENOPAUSE

Leanne McCarthy MD, FRCSC
• I have nothing to disclose
OBJECTIVES

• Cycle and hormonal changes prior to the final menstrual period (FMP)
• History of menopausal hormone therapy (MHT)
• Current consensus on menopausal hormone therapy (MHT)
• Diagnosis and management of Genitourinary Syndrome of Menopause (GSM)
• Impact of menopause on bone and cardiovascular health
• Impact of menopause on sleep and depression/anxiety
“The ovaries, after long years of service, have not the ability of retiring in graceful old age, but become irritated, transmit their irritation to the abdominal ganglia, which in turn transmit the irritation to the brain, producing disturbances in the cerebral tissue exhibiting themselves in extreme nervousness or in an outburst of actual insanity”

Written in 1887
Breast cancer risk linked to hormone therapy can persist for years, study says

By Jacqueline Howard, CNN

Updated 6:33 PM ET, Thu August 29, 2019

HAPPENING NOW
Michael Smerconish tackles the biggest news of the week. Watch CNN

CNN health

Take menopause seriously, support group urges after women report doctors ‘diminish’ concerns

Women ‘deserve quality of life,’ says founder of Menopause Chicks after study raises concerns

Karen Pauls · CBC News · Posted: Oct 25, 2019 7:00 AM PT | Last Updated: October 25

Wellness

A primer on perimenopause

What to expect in the years leading up to your last period

Dr. Melissa Lem · CBC Life · Posted: Mar 21, 2019 2:51 PM ET | Last Updated: March 21
WHY EDUCATION IS IMPORTANT

70% of women don’t have anyone to talk to about menopause. Let’s change that.
• 48 year old nulliparaous patient with heavy menstrual bleeding (HMB) secondary to uterine fibroids. Iron deficiency anemia some relief with oral iron. Wants to avoid any interventions. Asks if you can do blood work to assess menopausal status??
<table>
<thead>
<tr>
<th>Stages:</th>
<th>-5</th>
<th>-4</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
<th>+1</th>
<th>+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive</td>
<td>Early</td>
<td>Peak</td>
<td>Late</td>
<td>Early</td>
<td>Late*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopausal Transition</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopause</td>
<td>Early*</td>
<td>Late</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perimenopause</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of Stage:</td>
<td>variable</td>
<td>variable</td>
<td>variable</td>
<td>variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstrual cycles:</td>
<td>variable to regular</td>
<td>regular</td>
<td>variable cycle length (&gt;7 days different from normal)</td>
<td>≥ 2 skipped cycles and an interval of amenorrhea (≥60 days)</td>
<td>Amen x 12 mos</td>
<td>Amen x 12 mos</td>
<td>Amen x 12 mos</td>
<td>Amen x 12 mos</td>
</tr>
<tr>
<td>Endocrine:</td>
<td>normal FSH</td>
<td>↑FSH</td>
<td>↑FSH</td>
<td>↑FSH</td>
<td>↑FSH</td>
<td>↑FSH</td>
<td>↑FSH</td>
<td>↑FSH</td>
</tr>
</tbody>
</table>

*Stages most likely characterized by vasomotor symptoms  ↑ = elevated
MENOPAUSAL DIAGNOSIS

- Post hysterectomy/ablation
  - Symptoms and FSH
- IUD
  - FSH starting at 51/52 if 2 > 25 on 2 occasions 4 weeks apart- Remove
- On OCP
  - Stop pill x 2 weeks (2-4 recommended)
  - 7th day pill free not ideal
MENOPAUSE

- Permanent cessation of menstrual periods
- 12 months amenorrhea
- Median age 51.4
- <40 abnormal- Primary ovarian insufficiency (POI)
- Irregular cycles > 45 not need additional endocrine testing
Menopause
Symptoms and physical changes

- Headaches and hot flashes
- Hair becomes thinner and loses luster
- Teeth loosen and gums recede
- Skin becomes drier and develops a rougher texture
- Breasts droop and flatten
- Risk of cardiovascular disease
- Nipples become smaller and flatten
- Backaches
- Abdomen loses muscle tone
- Body and pubic hair becomes thicker and darker
- Vaginal dryness, itching and shrinking
- Stress or urge incontinence
- Bones lose mass and become more fragile
CONTROVERSIAL HISTORY OF HRT

• 20th Century- increased interest in menopausal disorder
  • “hormone deficiency syndrome”

• 1942- FDA approves Premarin for hot flashes
FEMININE FOREVER
by ROBERT A. WILSON, M.D.
The documented story of one of modern medicine’s most revolutionary developments and breakthroughs—the realization that menopause is a hormone deficiency and totally preventable. Now, almost every woman, regardless of age, can...
CONTROVERSIAL HISTORY OF HRT

• 1970- unopposed estrogen increases endometrial cancer
  • Later noted that addition of progestin helped
• 1988- FDA approved HRT for hot flashes and prevention osteoporosis
  • “healthy forever”
• 1998- Women’s Health Initiative
• 2002- increased CAD and Breast cancer with Estrogen and Progestin
• Present- negative impact on global perception HRT persists
CURRENT APPROACH TO HT: NAMS 2017

- Hormone therapy is the most effective treatment for VMS and GSM and has been shown to reduce bone loss and fracture
- Few medications have been as well studied for risk/benefit
- Net effect on all cause mortality in younger women is favorable
- Formulation, dose and route of administration should be determined individually and reassessed periodically
TYPICAL SITUATION

- 52 year old healthy female complains of severe flushes that are interfering with sleep and daily activities
- Has tried OTC products with no relief
- No period for 14 months
- She is healthy with normal blood pressure
- She is agonizing over information she has read online about risks of HT
Benefits of HT likely outweigh risks for symptomatic women who initiate HT <60 or within 10 years of menopause

Risks differ depending on type, dose, duration of use and route of administration

Treatment should maximize benefit and minimize risk

Periodic reevaluation of benefits and risks of continuing
## RISK FACTORS FOR BREAST CANCER

<table>
<thead>
<tr>
<th>Factor</th>
<th>Baseline Breast Cancer per 1,000 Women</th>
<th>Additional Breast Cancer per 1,000 Women</th>
<th>Total Breast Cancer per 1,000 Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>No HT use (baseline)</td>
<td>45</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>5 years HT use</td>
<td>45</td>
<td>2</td>
<td>47</td>
</tr>
<tr>
<td>10 years HT use</td>
<td>45</td>
<td>6</td>
<td>51</td>
</tr>
<tr>
<td>15 years HT use</td>
<td>45</td>
<td>12</td>
<td>57</td>
</tr>
<tr>
<td>Alcohol (2 drinks/d)</td>
<td>45</td>
<td>27</td>
<td>72</td>
</tr>
<tr>
<td>Lack of regular exercise (hr/wk)</td>
<td>45</td>
<td>27</td>
<td>72</td>
</tr>
<tr>
<td>Late menopause by 10y</td>
<td>45</td>
<td>13</td>
<td>58</td>
</tr>
<tr>
<td>BMI index (10 kg/m² increase)</td>
<td>45</td>
<td>14</td>
<td>59</td>
</tr>
<tr>
<td>Weight gain (≥20 kg)</td>
<td>45</td>
<td>45</td>
<td>90</td>
</tr>
<tr>
<td>Late childbearing and reduced breast feeding</td>
<td>45</td>
<td>45</td>
<td>90</td>
</tr>
</tbody>
</table>

BMI: body mass index; HT: hormone therapy.

Bélisle et al. JOGC. 2006;28:51-112.
STARTING ESTROGEN

- 0.625mg CEE (Premarin)
- 1mg 17-B estradiol (Estrace)
- 50mcg/day transdermal 17 B-estradiol
- 2 pumps 17- B estradiol 0.06%
STARTING ESTROGEN

• Transdermal is preferred to oral
• 17 B- estradiol vs Conjugated equine estrogen
• Lowest dose for symptom control
<table>
<thead>
<tr>
<th>Progestin Type</th>
<th>Daily Dose</th>
<th>Monthly Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micronized Progesterone</td>
<td>100mg</td>
<td>200mg</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>2.5mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Norethindrone</td>
<td>.35mg</td>
<td>0.7-1mg</td>
</tr>
<tr>
<td>Norethindrone Acetate</td>
<td>0.5-1.0mg</td>
<td>1.0mg</td>
</tr>
</tbody>
</table>
PROGESTIN THERAPY

- Different risk profiles of synthetic vs micronized progestin
- Micronized progesterone first line
- Micronized progestin 200mg 14 days q month ideal
- Levonorgestrel IUD
  - Excellent endometrial protection
  - Breast cancer risks unclear
TISSUE SELECTIVE ESTROGEN COMPLEX

- Bazedoxifene and CEE
- Endometrial protection with no Progestin
- Risk of DVT
  Patients at increased risk breast cancer
Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence

Collaborative Group on Hormonal Factors in Breast Cancer

Open Access • Published: August 29, 2019 • DOI: https://doi.org/10.1016/S0140-6736(19)31709-X
WHAT DOES THIS ARTICLE TEACH US?

• All Menopausal Hormone therapy increases risk of breast cancer (exception vaginal estrogen)
• Estrogen alone increases risk of taken > 5 years
• Risk for both current and past users
• Increased with increased duration of use
HOW COUNSELLING CHANGES WITH LANCET ARTICLE

- 1:200 risk with Estrogen alone
- 1:70 cyclic progestogen
- 1:50 continuous progestogen
MHT A SAFER & BETTER FUTURE

- Critical window hypothesis
- Use of transdermal estrogen
- Use of oral/vaginal micronized progesterone
- Use of LNG-IUD
- Local vaginal estrogen to improve vaginal health and sexual function

Davey 2018
FDA APPROVED INDICATIONS (NAMS2017)

- Vasomotor symptoms
- Prevention of Bone loss
- Premature hypoestrogenisom due to:
  - Premature ovarian insufficiency
  - Surgical menopause
TYPICAL SITUATION

• 52 year old healthy woman
• Has noted increased vaginal irritation over the past year
• Has tried several OTC treatments (yeast Rx, etc) with no relief
• Has significant pain with intercourse and now avoids intimacy with partner
• Uncomfortable discussing with doctor
GENITOURINARY SYNDROME OF MENOPAUSE
**GENITOURINARY SYNDROME OF MENOPAUSE**

- Atrophic Vaginitis
- Vulvovaginal atrophy
- Dryness
- Painful intercourse
- Urinary urgency and frequency
- Recurrent UTI
GENITOURINARY SYNDROME OF MENOPAUSE

Affects ~ 50% postmenopausal women
Other low estrogen states
Underdiagnosed and undertreated

CLOSER survey:
- 58%- avoid intimacy due to discomfort
- 64% loss of libido
- 64% experienced sexual pain
DIAGNOSIS

Clinical

Physical exam :

- External:
  - Scant pubic hair
  - Thinning and resorption of labia minora
  - Narrow introitus
- Internal:
  - Decreased vaginal caliber
  - Smooth/shiny/pale mucosa with loss of vaginal folds
  - Cervix flush with vaginal vault
  - Petechiae
Based on bother factor

General Measures:

• Avoid harsh soaps
• Incontinence pads not menstrual for leakage
• Lubricant for sexual activity
TREATMENT

- Lubricants and moisturizers
- Mild to moderate symptoms
- Always lubricant with intercourse (e.g., astroglide)
- Oils (limited data)
- Moisturizers (e.g., Replens, repragyn)
  - 2-3x per week on regular basis
For menopause sex discomfort, gel worked as well as hormone

Low-cost, over-the-counter moisturizers might be the best option for vaginal dryness

The Associated Press · Posted: Mar 19, 2018 12:54 PM ET | Last Updated: March 19, 2018
LOCAL VAGINAL ESTROGEN

- More effective and safer than systemic for GSM
- May require 8-12 weeks to get full benefit
- Caution in patients with hormone sensitive breast cancer
- Contraindication: undiagnosed vaginal bleeding
<table>
<thead>
<tr>
<th>Local Vaginal Estrogen</th>
<th>Estrone</th>
<th>Estragyn 0.1%</th>
<th>0.5-1g daily for 2 weeks</th>
<th>0.5-1g twice weekly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated Estrogen</td>
<td>Premarin</td>
<td>0.5g daily for 2 weeks</td>
<td>0.5g three times weekly</td>
<td></td>
</tr>
<tr>
<td>17B-estradiol</td>
<td>Vagifem</td>
<td>10ug daily for 2 weeks</td>
<td>10ug twice weekly</td>
<td></td>
</tr>
<tr>
<td>17B-estradiol</td>
<td>Estring</td>
<td>Change q 3 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ALTERNATIVE TREATMENT

• SERMS - not available in Canada
  • Good for those who cannot insert vaginal product
  • Systemic side effects

• Vaginal DHEAS
  • Potential for those that value avoiding estrogen
  • Not suitable with breast cancer on aromatase inhibitor
VAGINAL LASER

Similar short term improvement in vaginal epithelial maturation as local estrogen

Can consider in patients declining or with CI to local vaginal estrogen

Insufficient evidence to offer as equivalent to estrogen

No long term data

Cost

SOGC 2018
Midlife Aging
40 - 65 Years Old

The Menopause Transition
- Heterogeneous patterns of E2 decline and P4H rise
- Menstrual cycle irregularity
- Between-woman heterogeneity is related to factors such as race/ethnicity

↑ Depression and Anxiety
↑ Urinary Incontinence
↓ Cognitive Performance (After Menopause)
↑ Vasomotor Symptoms (Hot Flashes and Night Sweats)
↑ Sleep Complaints
↑ Cognitive Difficulties
↑ Vaginal Dryness
↑ Sexual Pain ↓ Sexual Desire

↓ Physical Function Performance
↑ Lipids ↑ Vascular Remodeling ↑ Metabolic Syndrome
↑ Body Mass Index ↑ Blood Pressure
↓ Bone Mineral Density
↓ Lean Mass ↑ Fat Mass

Changes in Physiological Systems and Functions

Window of Opportunity
+ Awareness
Adopt health behaviors
Design early preventive practices
CARDIOVASCULAR RISKS

- Postmenopausal state is risk factor for CVD
- Increase in LDL-C around final menstrual period associated with greater risk plaque presence after menopause
- High HDL is not consistently protective
- Menopause related fat redistribution relevant to CV health
- Increased FSH with low Estradiol associated with increase in carotid intima medial thickness
- Greater vasomotor symptoms adverse CV consequences

Khoudary 2019
CARDIOVASCULAR SCREENING

Assess and control Blood pressure

Address tobacco use

CV risk assessment every 5 years for women aged 40-75

Risk assessment using the modified Framingham risk score

Screen with:
- History and physical (waist circumference)
- Standard lipid panel (TC, LDL-C, HDL-C, TG)
- Glucose and eGFR

Canadian Cardiovascular Society 2016
Effects of hormone therapy (HT) on CVD vary depending on when initiated in relation to age and time since menopause

Less than 60 years and within 10 years of menopause

Observational data suggest reduced risk CVD in women less than 60 and within 10 years of menopause

Increased risk CVD when started later

CVD is not a contraindication to initiating HT
Multidimensional concept measured in different ways

30-40% prevalence (↑ in late peri menopause and natural post menopause)

Objective measures show improvement in sleep duration and deep sleep

Vasomotor symptoms have role but not only contributor

Poor sleep can adversely affect CV health
TREATMENT OF MENOPAUSAL SLEEP CONCERNS

- Rule out other sleep disorders
- Behavioral (CBT, Exercise, yoga)
- Herbal - isoflavones
- Sedatives (ezopiclone)
- SSRI/Gabapentin

Low dose Estrogen and Progesterone may help chronic insomnia (14 out of 23 articles show positive result)

- Progesterone - 300mg at bedtime

Attarian 2014 - Treatment of chronic insomnia disorder in menopause
BONE HEALTH

• “Postmenopausal bone loss” misleading
• Bone loss decelerates 2 years after FMP
• Lifestyle interventions for all:
  • Adequate calcium and vit D
  • Exercise
  • Smoking cessation
BONE HEALTH AND HT

Standard dose HT prevent bone loss in postmenopausal women

Low dose HT does NOT ↓ fracture risk

HT most appropriate bone active therapy if VMS and no contraindications

Option if alternate therapy not tolerated

NAMS 2017
Higher rates in perimenopausal

First time major depressive episode uncommon
- Risks: Prior MDD, antidepressant use, anxiety, premenstrual mood disorder, SES, menopausal symptoms

Increased depressive symptoms even without prior history

Proven therapeutic options first line

Estrogen therapy enhances mood in perimenopausal

Maki 2018
SUMMARY

• Menstrual cycle changes better indicator of MT than hormonal labs
• HT is most effective treatment for VMS and GSM and has been shown to prevent bone loss and fracture
• Benefits outweigh risk in symptomatic women <60 and within 10 years of menopause
• GSM is underdiagnosed and undertreated- local vaginal ET is 1st line
• Menopause has adverse effects on CVD and bone health
• Vulnerability for depression/anxiety with MT
• Sleep disorders are common in menopause- role for HT in treatment
ADDITIONAL RESOURCES

• NAMS position statement 2017
• www.menopauseandu.ca
• www.sigmamenopasue.com