Case Management of Special Populations in Perimenopause/Menopause

Hysterectomy; Surgical Menopause; POI;

Early; Breast and Endometrial Cancer

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Disclosures

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- Vitanica

Scientific Advisory Boards:

- Symphony Natural Health
- Integrative Therapeutics
- Nutritional Fundamentals for Health

Speaker's Bureaus:

- Doctor's Data
- NutraBiogenesis

Perimenopause/Menopause Fundamental Goals of Intervention

- QOL (peri/menopause specific)
  - HRQOL (health related) and GQOL (general)
- Do No Harm
  - Symptom relief with none to minimal impact on increasing risks of other diseases
- Disease Prevention/Risk Reduction
- Disease Management
- Opportunity for changes in health/life
- Education about health/Choices

Natural, premature, induced menopause

- *Natural* menopause occurs spontaneously
- *Premature* menopause occurs before age 40
  = POI (primary ovarian insufficiency) or primary ovarian dysfunction
- Induced premature menopause
  - bilateral oophorectomy (with or without hysterectomy), chemotherapy, pelvic radiation therapy, leuprolide or similar
- *Early* menopause (between ages 40-45)
  - natural; Bilateral salpingo-oophorectomy (BSO), chemotherapy, pelvic radiation, leuprolide or similar
- Surgical- be mindful of age of surgery and age of patient now; Hyst vs BSO vs both; Hx MHT or not/when/duration/details

Early Menopause

- Menopause between 40 and 45 years of age is called early menopause

- Causes:
  - bilateral oophorectomy
  - medical treatments- radiation, chemo, Lupron (menopause may be temporary)
  - woman's ovaries spontaneously stop producing eggs-underlying cause may not be found
  - Hysterectomy only (early about 25% of the time)
  - Unilateral oophorectomy (3.7 years earlier)
  - Embolization (+- 4 years early)

POI: Premature Menopause

- Causes: Cancer treatments (chemotherapy, surgery, radiation, hormonal therapies); surgical BSO; POI; leuprolide, smoking
- POI: A continuum of impaired ovarian function (intermittent to permanent) usually with extended periods of amenorrhea in women younger than age 40
- Primary ovarian insufficiency (POI)
- Consequences:

  - Typical menopause symptoms**
  - Earlier aging in general
  - Increased disease risks:

  Cardiovascular disease, osteoporosis, colon cancer, ovarian cancer, periodontal disease, tooth loss, cataracts, dementias, depression, OA

  * HT in adequate dosing will likely mitigate all these issues

Menopause Symptoms in POI

- 293 Chinese women with POI (in China)
  - Most prevalent symptoms were : mood swings (73.4%), insomnia (58.7%), sexual problems (58.7%), and fatigue (57.3%).
  - Moderate to severe mood swings (23.9%)
  - Itching (17.4%)
  - VMS (17.1%)

Women with POI tended to have more distressing menopause symptoms compared with women with natural menopause

Menopause J 2021;28(5):529

Primary Ovarian Insufficiency

- Primary ovarian insufficiency (POI)
  - Cessation of menstrual periods because of failure of the ovaries before age 40
  - Diagnosis: oligomenorrhea for 4 months or more; with 2 FSH levels (1 month apart), > 30
- Age-specific incidence of POI
  - 1% of women aged <40 y
  - 0.1% of women <30 y
  - 0.01% of women <20 y
    - May rise as childhood cancer survival increases
- Differences in prevalence by ethnicity
  - 1% of white; 1.4% of black; 1.4% of Hispanic; 0.5% of Chinese; 0.1% of Japanese women

Nelson LM. *N Engl J Med*. 2009;360(6):606-614; Falorni A, et al. *Clin Endocrinol (Oxf)*. 2012;77(3):453-458; Luborsky JL, et al. *Hum Reprod*. 2003;18(1):199-206.

Causes of early or premature menopause

Some possible causes include:

- **Unknown causes** –idiopathic premature menopause; in 90% of POI
- **Environmental**
- **Autoimmune conditions** – about 10 to 30 percent of affected women have an autoimmune disease: hypothyroidism, Crohn's disease, SLE, RA, MG,T1DM
- **Genetic conditions** – familial ovarian failure (FOF) and rarely galactosemia. 5-30% have an affected female relative, which suggests a genetic link:
  - Galactosemia-the unconverted galactose could be toxic to the ovaries.
  - Enzyme problems- ex/congenital adrenal hyperplasia
  - Other genetic conditions: ex/Turner's syndrome, Fragile X syndrome
  - Viral infections –inconclusive, possible=mumps or cytomegalovirus

Clinical Features and Diagnosis of POI

- Clinical features
  - Change in menstrual function (irregular menses and/or amenorrhea)
  - Estrogen deficiency symptoms
  - Symptoms masked if a woman is on HC

- Diagnosis
  - Menstrual disturbances such as oligomenorrhea or amenorrhea for ≥4 mo
  - FSH concentrations in the postmenopausal range (>25 IU/L) on two separate occasions, one month apart

European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI, et al.
***Hum Reprod*. 2016;31(5):926-937.**

Secondary Amenorrhea
Differential Diagnosis

- Pregnancy
- Hypothalamic amenorrhea
- Hyperprolactinemia
- Hypothyroid
- Hyperthyroid
- PCOS
- Primary ovarian insufficiency

Early and Premature Menopause Diagnosis- Medical History for DDX

- Menstrual history
- Family history
- Medication history
- Review of systems
- Other endocrine system problems
- Chronic illness
- Anorexia/bulimia
- Chaotic/disordered eating; radical diets
- Malnutrition
- Excessive exercise

Early and Premature Menopause Diagnosis- Physical Exam for DDX

- Physical exam
  - Secondary sex characteristics
  - Imperforate hymen
  - Sexual maturity
  - Vaginal patency; vaginal agenesis
  - Weight
  - Signs of hirsutism
  - Skin-acne
  - Head- hair loss

Clinical Evaluation in women with suspected POI

- Complete history and PE
- Family history of POI/early menopause
- LH, FSH, estradiol and prolactin
- If FSH initially elevated, repeat FSH and estradiol levels on at least 2 occasions, usually 1 month apart
- Karyotype (consider molecular cytogenetic studies of the X chromosome)
- FMR1 gene premutation testing
- Adrenal antibodies(evaluate adrenal reserve with ACTH testing if positive)
- TSH and thyroid peroxidase antibodies
- FBS
- Serum calcium and phosphorus concentrations
- Pelvic US

NOT INDICATED: progesterone withdrawal test, ovarian antibodies, ovarian biopsy

Premature/Early Menopause
Long term health consequences

- Persistent VMS
- Increased risk of overall mortality, cardiovascular diseases, neurological disease, early onset of bone loss, osteoporosis, fractures, GSM, mood disorders, dementia, stroke, Parkinson's, ophthalmic disorders.
- The risk of adverse outcomes increases with earlier age at the time of menopause.
- Includes the loss of estrogen,progesterone, testosterone and HPO feedback
- MHT can prevent some problems but not all.

Premature and Early Menopause CVD Risk

- CVD risk is elevated in women with POI and early menopause.
- Shorter reproductive lifespan- menarche to menopause < 30 years is associated with increased risk of CHD, CVD mortality and CHF.
- But... Is the increased CVD risk in this group attributable to premature loss of endogenous estrogen, or perhaps pre-existing heart disease risk factors contribute in some way to the early menopause.
- Possible genetic variants associated with early premature and early menopause, and the decline of AMH might also be related to a predisposition for CVD.
- Chicken or egg?

Evaluation- The bigger picture r.e. aging/prevention BSO, Early, Premature

- DEXA- at time of menopause onset; if has not had one- do it
- Expanded lipid panel
- FBS, A1c
- Physical exam

Hysterectomy Alone and CVD risks

- Hysterectomy alone may have different implications that BSO.
- 2005, (WHI-OS) = women with hysterectomy with or without oophorectomy had an adverse CVD risk profile at baseline and increased risk of CVD events.
- Hysterectomy itself is not considered a key determinant of CVD risk, but women with unfavorable CVD risks may more frequently undergo hysterectomy.
- **Take home:** need to recognize and treat CVD risks in this population.

Ovarian Failure after Hysterectomy

- Hysterectomy=most common non-obstetric surgery among women
- In U.S. up to one-quarter of women will have a hysterectomy before natural cessation of menses.
- Highest rates = 40-44 y.o.
- Two fold increased risk of ovarian failure after hysterectomy alone; and 20% or more will develop symptoms of diminished ovarian reserve within 1 year of simply hysterectomy

- About 3.7-6 years earlier on average
- It remains unresolved whether the increased risk is attributable to the surgery itself or to the underlying condition that was the indication for the hysterectomy.

Menopause after Bilateral Salpingectomy

- Bilateral salpingectomy (BSO) at the time of hysterectomy is proposed as a possible preventive strategy for ovarian cancer.
- A retrospective observational cohort study – Sweden; a hysterectomy for a benign reason, with or without OBS.
- Results: increased risk of menopause 1 year after salpingectomy with hysterectomy vs hysterectomy only J Obstet Gyn 2019;220(1):85

- Why consider this surgery: A meta-analysis of three studies evaluated whether BSO at the time of benign hysterectomy decreased the risk of high grade serous carcinoma (HGSC) and primary peritoneal cancer. The researchers found a 49% reduction in women who underwent OBS vs those who did not.

Eur J Cancer 2016;55:38

Menopause-Salpingectomy 2020

- Prophylactic salpingectomy: no difference in time to the first physician visit related to menopause for both women who underwent hysterectomy with OS and women who underwent OS for sterilization.
- Author conclusions: the theoretical risk of premature menopause via thermal injury to the ovary or disruption of ovarian blood supply is not significant enough to be detected

Am J Obstet Gynecol 2020;223(2):221

Hysterectomy/Embolization

- Premature menopause -inadvertent sequela of hysterectomy or uterine artery embolization
- Hypothesized to be due to compromised ovarian blood flow.
- One report from 1985: 45.4 + - 4 years

Farguhar C. BJOG 2005;112

Tulandi T. Ob Gyn 2010;115

Menopause After Hysterectomy or Unilateral oophorectomy

- **3.7 years earlier: The average onset age of menopause in those who underwent hysterectomy is 3.7 years earlier than average even when the ovaries are preserved.**
- **Why? possibilities:**

  -disruption of blood supply to the ovaries

  -missing endocrine feedback of the uterus
- The function of the remaining ovaries is significantly affected in about 40% women
- A similar and only slightly weaker effect has been also observed for endometrial ablation
- Issues: usual menopause sx, cardiovascular and osteoporosis risks, prolapse, incontinence

IF USO: menopause onset only slightly earlier (about 1 year)

Hum Reprod 2014;29:835-841.

Surgical Menopause: Bilateral Oophorectomy

- BO is associated with immediate menopause symptoms: VMS, urogenital atrophy, sexual dysfunction, sleep disturbances and mood affects... All can severely affect her QOL.
- Long term, early surgical menopause (40-45) increases risk of osteoporosis, CVD, cognitive impairment and mortality

Surgical Menopause

- BSO– definitive and abrupt onset of menopause= usually, but not always associated with higher rates of CHD morbidity and all cause mortality particularly in women aged 45 years or younger at the time of surgery, who were not subsequently treated with estrogen therapy.
- ACOG: encourages ovarian conservation at time of indicated hysterectomy
- Most expert groups recommend estrogen therapy until the time of anticipated natural menopause; other considerations warrant longer...(to be discussed more).

Surgical Menopause
Mortality and Cardiovascular Disease

- Mayo Clinic Cohort Study

  increased all cause mortality

  in women who underwent prophylactic BSO before age 45 years who did not take ERT

Lancet Oncol 2006;7

Surgical Menopause

Mortality and Cardiovascular Disease

- Danish Cohort Study
  - increased risk of IHD among women who had a BSO before age 40 vs after age 45
  - smaller increased risk for IHD among women who experience natural menopause before age 40
  - ERT =significant protection against IHD
    - most pronounced for current users and for women if ERT started within 1 year after surgery

Maturitas 2006;53

Surgical Menopause

Mortality and Cardiovascular Disease

- Nurses' Health Study
  - 30,000 women
  - Hysterectomy with BSO before age 45 years =increased risk for CHD
  - Oophorectomy at any age was associated with an increase risk of death, including CHD and lung cancer deaths

ObGyn 2009;113

Surgical Menopause Cardiovascular

- Surgical menopause was associated with a higher mean FRS compared with natural menopause. Compared with women with age at natural menopause from 50-54 years (10.2% CVD risk)
- Natural menopause before aged 40=12.2% CVD risk
- Natural menopause age 40-44= 11.4% risk
- Natural menopause 45-49= 10.6% risk

Meaning: earlier the BSO, the greater the CVD risk (without HRT)

Menopause J 2021;28(5):484-490

Surgical Menopause
Neurologic

- Increased cognitive impairment or dementia if BSO before natural menopause
- Risk increased if younger age at BSO
- Only in those who did not take ERT after surgery and until at least age 50
- Increased risk of parkinsonism- and worse if younger age at BSO

Mayo Clinic Cohort Study 2007

Surgical Menopause
Neurologic

- Poor performance on memory tasks
- Decreased global cognitive functioning scores
- Decreased memory scale scores

Surgical Menopause Cognition

- Surgical menopause;randomized to 10 mg estradiol valerate injections or placebo (physiologic and supraphysiologic doses).
- Compared with preoperative assessment and 6-7 months of f/u= cognitive function was stable among women receiving infections but decreased among women on placebo

Psychoneuroendocrinology 1988;12:345

Psychoneuroendocrinology 1992;17:485

Surgical Menopause Cognition 2021

- 18 month prospective study-57 women BSO.
- Objective: assess changes in cognition associated with surgery and the impact of HRT
- Results: self reported perceived cognitive function declined in HRT users and non users at 6 months post op..
- 18 mo, cognitive function increased to baseline -HRT users and non users
- Why difference results than previous studies?

1) self reported outcomes vs mental status testing 2) short f/u period 3) changes in memory and cognition may take years to manifest and may not be detected during within 18 month 4) lack of detailed information on HRT use and doses 5) possible that women with more severe menopause symptoms were prescribed HRT and the 6 month f/u could have reflected more severe symptoms in that group.

Menopause J 2021;28(4):349

Surgical Menopause
Mood

- Cohort study of Danish female nurses
- Bilateral oophorectomy at age $\geq$ 51 years, but not younger, was associated with a slightly higher rate of depression compared to women with ovaries at that age

Menopause J 2022; 29(3):276

Surgical Menopause
Mood and Sexual Function

- Increased long-term anxiety; worse if younger ages (before age 49)

  -ERT did not modify risk
- Increased depressive symptoms- but weaker

Mayo Cohort Study

Surgical Menopause
Mood and Sexual Function

- TAHBSO (Total abdominal hysterectomy bilateral salpingo-oophorectomy) =significantly greater anxiety and depression
- If ERT- less anxiety and depression and similar to women with ovaries.
- More impaired sexual function

  no change with ERT

J Psychosom Obstet Gynaecol 1993

Surgical Menopause
Mood and Sexual Function

- Hysterectomy with BSO = low sexual desire, less likely to be sexually active and more likely to be dissatisfied with their sex life and partner relationships.
- Women younger than 50 with BSO were twice as likely to have low sexual desire compared with premenopausal women.
- Significantly improved with hormone therapy

J Sex Med 2006;3

Surgical Menopause- Skin aging

- Objective: assess the effects of hysterectomy and BSO compared with the effects of hysterectomy alone on skin aging in premenopausal women undergoing hysterectomy for benign conditions .
- Results:
  - All skin parameters in the hysterectomy group and the hyst/BSO group worsened on weeks 24 and 48.
  - Laxity/sagging and texture/dryness scores on weeks 24 and 48 were significantly worse in the BSO group
  - Laxity/sagging and texture/dryness scores continued to worsen between 24 and 48 weeks.
  - Scores for the QOL index were significantly higher in the BSO group compared with the non-BSO group

Emrah T. Menopause 2015;23(2)

Surgical Menopause
Osteoporosis

- Accelerated bone loss
- Before age 45- significant risk factor
- Even after natural menopause- increased risk
- ERT prevents bone loss
- ERT reduces fracture risk

Surgical Menopause Perspectives and Decisions

- Women need to know ahead:
  - sudden and severe symptoms: VMS, lack of sleep, mood swings, anxiety, depression, flat emotions, vaginal itch/dry/pain, low libido, SI/UI, weight gain, hair changes, arthritic pains, fatigue

HT Clinical Guidelines NAMS
Special Populations

- **"Early" Menopause= POI/surgical**

POI or premature surgical menopause (< age 52) without CIs:

-HT until at least 52y.o.

(benefits outweigh the risks for effects on bone, heart, cognition, GSM, sexual function and mood.)

Increased risks if no ET: osteoporosis, dementias, heart disease, stroke, Parkinsons, ophthalmic disorders, overall mortality

HT Clinical Guidelines NAMS
Family History of Breast Cancer

- Use of HT **does not** further alter the risk for breast cancer in women with a FHx of breast cancer

Women at High Risk for Breast Cancer

- Women with a higher risk of breast cancer because of FHx: data suggest that the use of systemic ET does not increase the risk of invasive breast cancer.
- WHI: CEE in women with an affected first degree relative was not found to significantly increase risk of breast cancer compared with those receiving placebo
- Two Sister study: neither systemic ET nor EPT was found to elevate the rate of breast cancer diagnosed before age 50 in sister of women with invasive or in situ breast cancer.

HT Clinical Guidelines NAMS
BRCA positive without Breast Cancer

- If BRCA positive without breast cancer

- If BSO: * Systemic ET or EPT does not increase the risk over baseline if FHx and if BRCA 1 or 2
- If BSO: no history of BC; no increased risk after 7.6 years if ET; nonsignificant increase if EPT
- VET for GSM- does not elevate risk

- Benefits of ET to decrease health risks caused by premature of estrogen (or lower estrogen levels due to BSO no matter age of BSO)
- Consider systemic HT until the median age of menopause, or longer based on individualized assessment.

HT Clinical Guidelines NAMS

Breast and Endometrial Cancer Survivors

Bothersome VMS- consideration of systemic HT

- *Survivors of endometrial and breast cancer*: consider nonhormone therapies
- *Survivors of endometrial cancer* (prior early endometrial cancer treated with hysterectomy): if VMS not well controlled with nonhormone therapies, consider systemic HT (consult oncologist)
- *Survivors of breast cancer (ER positive):* systemic HT only for compelling reasons after nonhormone options have been unsuccessful; counsel thoroughly; shared decision; consult oncologist.

  2 RCTs= conflicting outcomes; 1=elevated risk of recurrence after 2.1 years and 4 years . 2=no effect after 4.1 year and 10.8 years but increased risk in contralateral breast.

DCIS

- DCIS and bilateral mastectomies- MHT safe; risk of invasive disease post bilateral mastectomies in that setting is so low
- DCIS and lumpectomy or unilateral mastectomy : still a risk factor for invasive disease and generally MHT is CI
- Most DICS is HR+ but if HR- DCIS probably reasonable to give if other factors indicate need

HT Clinical Guidelines NAMS
Breast and Endometrial Cancer Survivors

<u>Bothersome GSM symptoms- consideration of low dose vaginal ET</u>

- *Low dose vaginal ET:* minimal systemic absorption (blood levels in the post menopause range; minimal to no demonstrated risk for recurrence of endometrial or breast cancer.
- *Hx Early endometrial cancer/ post hysterectomy:* low dose vaginal ET for relief of GSM if non hormone options are not successful (tori: vaginal ET or non hormone options)
- *Hx breast cancer:* low dose vaginal ET generally considered safe (ring, tablets, suppositories, E3); involve the woman's oncologist, especially if on AI

GSM; Use of low dose Vaginal Estrogen History of Breast Cancer- ACOG

- ACOG committee opinion March 2016

-Experiencing urogenital symptoms

-Reserve vaginal estrogen for those who are unresponsive to nonhormonal therapies

- Make decision/recommendation in concert with woman's oncologist
- Informed decision-making and consent
- **Data do not show an increased risk of cancer recurrence among women currently undergoing treatment for breast cancer or those with a personal history of breast cancer**

ACOG; 2016; number 659

GSM Management in high risk breast cancer or with breast cancer NAMS/ISSWSH 2018 consensus

General guidelines

- individualized tx, taking into account risk of recurrence, severity of symptoms, effect on QOL and personal preferences
- Moisturizers and lubricants, pelvic floor pt and dilator therapy are first line treatments
- Involve the treating oncologist in decision making when considering local hormone therapies
- Ospemifene, an oral SERM- has not been studied in women at risk for breast cancer and is not FDA approved for use in women with or at high risk for breast cancer
- Off label use of compounded vaginal testosterone or estriol is not recommended
- Laser therapy may be considered in women who prefer a nonhormone approach; women must be counseled regarding lack of long term safety and efficacy data

GSM Management in high risk breast cancer or with breast cancer NAMS/ISSWSH 2018 consensus

- Women at high risk for breast cancer
  - try non hormonal option; if inadequate
  - local hormone therapies are a reasonable option
  - No increased risk of breast cancer with systemic or local estrogen therapies beyond baseline risk

GSM Management in high risk breast cancer or with breast cancer NAMS/ISSWSH 2018 consensus

- <u>ER positive breast cancers on Tamoxifen</u>
  - small transient elevations in serum hormone levels noted with local hormone therapies in women on tamoxifen are very low
  - If persistent, severe symptoms and have failed nonhormone treatments; and if low risk of recurrence, consider local hormone therapy

GSM Management in high risk breast cancer or with breast cancer NAMS/ISSWSH 2018 consensus

- <u>ER positive breast cancer and on AI</u>
  - AIs result in undetectable serum estradiol levels; transient elevations in estradiol levels may be of concern
  - GSM symptoms are often more severe
  - If severe symptoms and have failed nonhormone treatments- consider local hormone therapies; consult with her oncologist; consider switching to tamoxifen

GSM Management in high risk breast cancer or with breast cancer
NAMS/ISSWSH 2018 consensus

- Triple-negative breast cancers
  - Theoretically ok; no data for women with metastatic disease
- Metastatic disease
  - women with metastatic disease may have QOL GSM issues to address- consider if comfort and intimacy is a priority
  - if probable extended survival , local hormone therapy may be considered; if limited survival then QOL may be more of a priority

GSM-local Hormone Options
Breast Cancer/Endometrial Cancer

Vaginal DHEA

- Vaginal DHEA 6.5 mg (0.5%)- FDA approved for postmenopausal women with moderate to severe dyspareunia due to VVA.
- RCT of survivors (mostly breast), w/moderate to severe dryness or dyspareunia: 3.25 mg vs 6.5 mg vs placebo daily for 12 weeks; neither dose showed improvement in dryness/dyspareunia, but 6.5 mg did improve sexual health on the FSFI (Female Sexual Function Index).

Support Care Cancer 2018; 26:643

- Slight but statistically significant increase in plasma estradiol and testosterone. FDA product has not been studied in breast cancer survivors; label warns against use. No studies comparing vaginal DHEA to vaginal estrogen

GSM-local Hormone Options
Breast Cancer/Endometrial Cancer

- Vaginal testosterone
  - only compounded products available
  - One trial; 80 healthy postmenopausal women for 12 weeks with a compounded vaginal cream of 300 mcg testosterone propionate improved vaginal signs and symptoms.

Menopause 2016;23:792

- Consider vaginal testosterone Rx in women with breast cancer history, to those who are currently taking an AI, which blocks this conversion; due to AI blocking conversion of testosterone to estradiol.
- But...of In 2 of 3 trials, serum testosterone levels were not fully characterized, and the third, serum testosterone reached supraphysiological range after 4 weeks, despite that the women in the third trial were taking an AI (12% had persistently elevated estradiol levels as well).

Sex Med 2014; 2:8
Oncologist 2011; 16:424
JAMA Oncol 2017; ;3:313

GSM-local Hormone Options
Breast Cancer/Endometrial Cancer: FDA

Vulvovaginal Estrogens

- Most breast cancer prevention and tx strategies focus on lowering or antagonizing ambient estrogen concentrations. All strategies: SERMS--, BSO, GnRH agonists or AIs =goal: to reduce the estrogen environment to lower breast cancer risk. Both systemic and local estrogen based treatments are controversial and discouraged, for women with a history of or are at high risk of breast cancer. (NAMS AND ACOG AND ISSWSH **DO NOT AGREE with this**)

- **The FDA** approved prescribing information cites a prior history of breast cancer is a CI to estrogen-systemic or local.
- Absorption of local ET varies by 1) **active ingredient**: CEE > estradiol > estrone > estriol. 2) **amount of active ingredient** 3) **surface area** =greater surface area in the vagina are more readily absorbed than vaginal tablets or rings 4) **bioadhesives** are less absorbed than those with penetration enhancers 5) **condition of vagina=** more atrophic/thin... Highly absorptive; diminishes with estrogenization

5) **location-** lower one third of the vagina preferred over the upper two thirds, due to the vascular connection with the uterus in the upper vaginal and potential for greater systemic absorption; if estrogen is applied to the vulvar skin/vestibule vs the highly absorptive vaginal epithelium.

- Local vaginal estrogens have inconsistently increased serum estradiol levels- thus lack of clarity-
- Observational studies : relative safety of local ET; definitive placebo-controlled, RCT data lacking.
- WHI and a large Finnish observational study=no elevated risk of breast cancer.
- One case control study: ocal ET was not associated with an increased risk of recurrence in women with a history of breast cancer.

GSM-local Hormone Options
Breast Cancer/Endometrial Cancer

Lidocaine

- N=46 postmenopausal breast cancer survivors with severe GSM, dyspareunia, increased sexual distress scores, sexual dysfunction;
- Tx: topical 4% aqueous lidocaine- apply on a cotton ball to vestibule for 3 minutes before vaginal penetration- 88% reduction in dyspareunia vs 33% reduction with saline.

J Clin Oncol 2015;33:3394

HT: Determining Risk vs Benefit

- 8 most important factors=

1. The age at initiation of hormone therapy: years since menopause, therapeutic window
2. Dose of estrogen
3. Route of administration
4. Type of progestogen
5. Type of estrogen
6. Estrogen alone or with P
7. Duration of HT
8. Considerations for women > 65

HT Clinical Guidelines NAMS 2022
General

- HT=most effective treatment for VMS and GSM
- HT has been shown to **prevent** bone loss and fracture
- Benefits are most likely to outweigh risks:

  - symptomatic women who initiate HT when < 60 y.o. or

  - symptomatic women within 10 years of menopause onset

HT Clinical Guidelines NAMS 2022
General

- HT should be individualized
  - indications
  - treatment goals
  - age
  - time since menopause
  - time since initiation or last d/c of HT
  - personal health risks; past HT experiences
  - preferences
  - balance of B vs R or HT vs non hormone options

HT Clinical Guidelines NAMS 2022

General

- Risks of HT differ overall for ET and EPT
- More favorable safety profile for ET
- Use an appropriate HT type, dose, formulation, route of administration, and duration of use to meet treatment objectives
- Periodic reassessment of changes in a woman's health, and anticipated benefits, risks and treatment goals over time

HT Clinical Guidelines NAMS 2022
General

- Assess risk for estrogen-sensitive cancers, bone loss, heart disease, stroke and VTE
- Decisions about HT should be incorporated into lifestyle modification to manage symptoms and risks for chronic diseases of aging
- (and I would add: should be incorporated into select nutrients/botanicals/other natural interventions for symptom management, disease prevention and treatment)

HT Clinical Guidelines NAMS 2022
FDA-approved Indications

- VMS
- Prevention of bone loss
- Hypoestrogenism (hypogonadism, castration, POI)
- GSM/Vulvovaginal atrophy

HT Clinical Guidelines NAMS 2022 Formulation, Dosing, Routes, Safety

Initiation/Duration of use

- If POI, early natural or induced menopause, surgical menopause before age 45, and esp before age 40, (and are otherwise candidates for HT):
  -initiate HT early if not CI; option for OC in women < 40
  -continued use at least until the median age of menopause (52)
  (tori: if surgical menopause- continue long term)

Basis: potential prevention of risks related to early estrogen loss on CHD, osteoporosis and increased fracture risk, cognitive and mood changes, sexual dysfunction, GSM, increased risk for dementia/open angle glaucoma, depression and poor QOL

* note: preserve ovaries if hysterectomy for benign conditions and average risk of ovarian cancer.

POI- Management

Hormone replacement for young women with POI should mimic normal ovarian function as much as possible; and adequate doses of estrogen with adequate endometrial protection.

Options:

Ex/ td estradiol patch 0.1 mg+OMP 200 mg/day or MPA 10 mg/day for 12 days/month

Ex/ Femring q 3 months (0.1mg)+OMP 200 mg/day or MPA 10 mg/day for 12 days/month

Ex/ Oral Estradiol 2 mg/day + OMP 200 mg/day for 12 days/mo

Ex/ OCP (EE 20 or 30 mcg/progestin pill; cyclic or continuous ; better to have cyclic regimen-easier to recognized the 5-10% chance for spontaneous pregnancy

(recent evidence demonstrated that 0.1 mg patch plus MPA or 2.0 mg Estradiol + MPA or 1.25 CEE was equal to or superior to a 30 mcg OCP in improving BMD in women with POI)

(but 30mcg OCP more effective than 0.625 mg CEE + MPA in BMD L spine)

Prothrombotic Mutations and systemic HRT

- Most guidelines for oral HT and prothrombotic gene mutation.= CI
- Annual incidence of VTE in all women with FVL is 0.5%. Heterozygotes for the gene mutation= 4 to 10 fold increased risk of thrombosis compared with homozygotes who have a 50 to 100 fold increased risk.
- The relative risk of developing a VTE is 3% to 8%, (a moderate risk factor) compared with other stronger risk factors (hip fracture, major trauma or general surgery
- VTE is multifactorial; consider modifiable or nonmodifiable risk factors such as obesity, smoking, DM, hyperlipidemia, HTN, personal or family history of thrombosis, cancer, and age when assessing risk.

-Ex/women who are obese have a 2 to 3 fold higher risk of VTE; severe obesity, even higher.

-Approximately 25% of FVL carriers with a strong family history of VTE have at least one thrombotic event by age 50.

-For perimenopausal women, the annual rate of VTE is 2 to 2 per 1,000.

-Venous thrombosis increases after age 40; rises dramatically after age 45; approximately doubles each decade; rates = about 5 to 6 per 1,000 annually by age 80.

Prothrombotic Mutations and systemic HRT, continued

* OCPs and FVL results in a 34 fold increased risk of thrombosis.

- estrogen composition in OCPs is different (and much higher), than oral HT, but concern with VTE and HRT still exists.

- 3 trials confirmed an increased risk of thrombosis in women who carried the FVL mutation when taking HT containing CEE and MPA. In women with CAD= up to 14 fold increase in VTE in FVL carriers using oral CEE/MPA.
- Largest of the trials, the WHI, calculated the absolute risk of VTE with oral CEE and MPA to be 0.8% annually, and the risk was only marginally increased with CEE alone. All the studies found that the risk of VTE was highest in the first year of HT use.
- Several large population based case control studies : no increased risk of VTE with td estrogen, with or without progestogens.
- ESTHER study : The rate of VTE in women with either FVL or another prothrombotic mutation (PT G20210A) using transdermal estrogen was similar to women with a mutation not using HT ; an almost 25 fold increase in VTE in women with a prothrombotic mutation using oral estrogen.

- **Tx Options:**

1) solve VMS or other menopause symptoms with a non estrogen containing product (Herbs, nutra, SSRI, gabapentin)

2) Joint decision- transdermal ET. (alter other risks) the worst case scenario would be an increased risk of VTE from 0.8% to 1.5% annually. No RCTs on VTE risk using td estrogen in women who carry the FVL mutation. (FYI- WHI showed that low dose aspirin are not effective for primary prevention of VTE in FVL carriers using HT).

Which patients get what?

- Surgical menopause

  -typically have more severe symptoms

  -estrogen/testosterone/DHEA; no progesterone needed if no uterus

  -optional deliveries

  - if no ET, then earlier mortality, more osteoporosis, CVD and possibly AD

Which Patients Get What?

- Early Menopause
  - MHT until age 51; cons/longer if needed for symptom relief or disease prevention
- POI
  - MHT until age 51(twice average menopause doses- or OCPs) ; cons/longer if needed for symptom relief or disease prevention

Case #1: Menopause; Hx Breast CA; VMS

- 60 y.o. postmenopausal woman; 5 years stage II breast cancer survivor; post treatment
- Severe VMS
- No relief or unacceptable side effects from all meds and botanicals
- Have the botanical doses/products been adequate?

Case #2: Menopause; Breast Ca survivor
GSM and VMS

- 55 y.o. postmenopausal woman; stage I breast cancer x 2 years post treatment;

  Meds: Tamoxifen
- Severe atrophic vaginal changes and VMS

Case #3 Early age menopause; Tamoxifen; Menopause symptoms

- **Age = 43.** Premenopausal and now perimenopausal due to **breast cancer** - post surgery/radiation/ **chemo**
  - **Sx: VMS, Dysthymia, joint pains, vaginal dryness**
  - LMP 42 y.o. (9 mo. Ago; spotting now x 3 days)
  - No other chronic health problems
  - overweight
  - Tamoxifen daily
  - What I need to know: symptoms; Menstrual history; FH-AD, premature CVD, osteoporosis-fx? Weight? Other...

Clinical Scenario #3 continued

- VMS/MCI/Dysthymia/ joint pains
  Black cohosh 40 mg S.E. bid
  Bacopa 500 mg/day
  Soy 60-100 mg/day (avoid > 150 mg)
  SJW 300 mg tid or SAME 200-600 mg/day

- Atrophic VV/dyspareunia- with itching, pain at introitus/dryness with penetration
  Moisturizers tiw; consider Vaginal estriol biw

- Considerations:
  A) Early perimenopause/menopause due ??to age of 43
  - proactive bone health + DEXA; D, Ca/Mg, other; weight bearing exercise
  - proactive brain aging- Bacopa; Mind diet; stress reduction
  - proactive cardiovascular aging- fish oils, Mediterranean diet; regular exercise
  B) overweight – weight loss plan- benefits breast cancer recurrence risk, CV risk

Case #4: Vulvovaginal Atrophy in Breast Cancer Patient/Perimenopausal

- 48 y.o. woman; LMP 9 months ago; 1 year breast cancer survivor; Tamoxifen now

  - Symptoms: severe vulvovaginal atrophy, dyspareunia-dryness, pruritus. No systemic symptoms

  - Tx options:

    OTC Vaginal moisturizer

    "Natural moisturizers"

    Vaginal/vulvar estrogens= estriol suppositories, estriol cream, Estring, Estradiol tablets (Vagifem)

    Vitamin E suppositories

    Lubricants prn

    Ex/ Estriol 1mg/gm. Insert 1/2gm and apply ½ gm daily for 2 weeks then a maintenance of twice weekly.

Breast Cancer Patients
VVA Options

- Vaginal moisturizers/lubricants
- Vaginal hyaluronic acid/E/A= Ovuli
- Vaginal Fennel cream
- Vaginal DHEA
- Vulvo/Vaginal estriol suppositories or creams or capsule
- Vaginal estradiol soft gel

Case #5:newly diagnosed breast cancer Hx Hx 20 years long term ccHRT

- 69; newly diagnosed invasive ductal breast CA
- Low dose ccHRT (continuous combined) creams and then oral since 54 y.o.
- Sx history without HRT: severe VMS, depression, irritable
- FH: m=severe osteoporosis
- Fear of D/C HRT and return of symptoms

Case #6: Postmenopausal; Dyspareunia; Family CA Hx

- 52; 3.5 years postmenopausal
- Dyspareunia; VMI every hour day/night
- Nocturia x2 and daytime frequency
- HRT questions
- PMH: multiple precancerous colon polyps
- FHx: M=Breast Ca age 70 (DCIS)
  F= T2DM; precancerous polyp
  PGM= colon cancer
  PGM 2 siblings= colon CA

Case #7: young surgical menopause Menopause symptoms

- 29y.o.
- TAHBSO aged 27- menometrorrhagia/dysmenorrhea with previous history
- **history 3 laparoscopies-endometriosis** treatment
- Current symptoms:

  severe night sweats, HSDD, deep dyspareunia and pelvic pain after orgasm

* HT after surgery- couldn't afford what was prescribed= vivelle 0.1 and d/c after 8 mo. ; none now for 16 months

Case #7 cont: young surgical menopause

Problem areas:

1) Surgical menopause= VMS, HSDD, dyspareunia; bone/heart/brain aging
2) History of endometriosis x 3

She needs systemic ERT (estrogen and testosterone), but what about endometriosis?

Case #7 cont: young surgical menopause

1) **Surgical menopause= VMS, HSDD, deep dyspareunia**

   Tx: her age warrants twice average ERT doses; but history of endometriosis– go with OCPs.

   OCPs- VMS, HSDD and the high dose progestin will hopefully prevent recurrent of endometriosis

Case #8
Surgical Menopause; Strokes, FHx

- 61 y.o. woman
- Surgical menopause age 45 (benign reason)
- On oral CEE and now estradiol 1 mg/day ever since
- 2 strokes (1=hemorrhagic; 2-occlusive)
- Several TIAs
- Osteoporosis hip and osteopenia spine
- Mother= Parkinson's, early MI and by-pass; Father = early strokes and MI- died 48; 2 brothers= strokes in 40s. None were smokers

- ERT: Benefits vs Risks????

Case #9 Early Menopause

- 44 now; LMP=age 41 (3 years ago)
- Asymptomatic
- Does she need ET or not???

Case #10: 43; Serous Cystadenoma Menopause symptoms

- 43 y.o.
- One year ago: unilateral oophorectomy and bilateral salpingectomy
- diagnosis= serous cystadenoma/pre-cancer
- Now: enlarging cyst on remaining ovary; scheduled for oophorectomy
- LMP 12 months ago- minimal VMS; very moody/throwing things/yelling; dyspareunia due to dryness; clitoral pain with being touched/orgasm
- Issues: she is in Early Menopause

  she will soon be surgically menopausal

Decisions: HRT or not?

hysterectomy along with upcoming surgery, or not?

43; serous cystadenoma
Menopause Management strategy

- Early Menopause : increased risk for CVD, Osteoporosis, AD, more HRT until **52**
- Surgical Menopause: increased risk for CVD, osteoporosis, AD, more HRT until **52** (per NAMS); other opinions= life long
- No uterus: could take estrogen only
- Rx plan: **Now**= estradiol patch 0.05 mg 1x/week + OMP 100 mg/d

  After oophorectomy: continue above R

  If also hysterectomy: estradiol patch only; no OMP needed

  Also:

  1) Estriol suppositories 1 mg- insert nightly for 2 weeks then biw
  2) Estriol cream 2 mg/gm- apply ½ gm vulva nightly for 2 weeks then biw

F/U one month

Case #11 Ovarian Cancer

- 45 y.o. hysterectomy/bilateral oophorectomy/lymphadenectomy/tumor debulking with minimal residual disease for stage III epithelial ovarian cancer. Now on chemotherapy
- Sx=incapacitating hot flashes
- Tx=Nonhormone tx: Failed venlafaxine, gabapentin, CBT, hypnosis, paroxetine, clonidine.
- 1991: Overall survival and disease free survival were comparable HT and non HT users groups
- 2001: 21% recurrence in HT users and 31% recurrence in non users.
- One RCT 1999 ; DFS and OS were similar between the two groups.
- 2006: women using HT after treatment for EOC had a lower risk of dying compared with non users. These survivor results were correlated only to serous tumors
- 2015: in patients with EOC, postoperative HT did not have a negative effect on OS and tumor recurrence.
- **Overall: SAFE; limited data**

- **BUT** ...tumors that are likely to contain estrogen receptors=low grade serous carcinomas and sex cord stromal malignancies such as ovarian granulosa cell and Sertoli-Leydig ovarian tumors– however, date is very limited

Case #12; Surgical Menopause/Endometrial Cancer case

-*Age 60; LMP 52; endometrial cancer and H/BSO 6 months ago*

-*Symptoms: moderate VMS*

-*Survivors of endometrial cancer*: consider nonhormone therapies

-*Survivors of endometrial cancer* (prior early endometrial cancer treated with hysterectomy: if VMS not well controlled with nonhormone therapies, consider systemic HT (consult oncologist)

-BSO: needs bone/heart/brain aging protection

Case #13

Recent TAHBSO/early stage endometrial cancer; PCOS

- A 45-year-old black woman; severe VMS ; no relief with self tx; HTN, obesity
- PMH: TAHBSO 6 months ago; infertility, PCOS, obesity (BMI=50); stage 1 endometrial CA

Case #13
Considerations

- Clinical challenge: severe VMS but endometrial CA
- PCOS: lifelong disorder and increased cardiometabolic risk factors= (obesity, T2DM, dyslipidemia, HTN= 4x greater risk of CAD and stroke.
- TX goals: weight loss, manage HTN, address QOL (VMS); avoid increased risk of recurrence

Case #13
HT Considerations

- Largest DBPT: 1 or occult Stage II endometrial cancer: Outcomes for systemic ET versus P were the same for disease recurrence, development of a new malignancy, all-cause mortality, and death.
- Another study: Black women were found to have an increased risk of disease recurrence when treated with ET.
- ET for QOL can be considered
- ET due to BSO and increased risk of osteoporosis/CVD/Dementia if no ET
- Discuss risks and benefits before starting ET therapy.
- ET RX: transdermal estradiol half average dose

1) Estradiol cream -1 mg/gm; apply ½ gm daily

or

1) Estradiol patch 0.025 mg once weekly

Case #14 POI case

- 38 y.o. and LMP 1 year ago; Diagnosis POI after workup
- Hormone replacement for young women with POI should mimic normal ovarian function as much as possible; and adequate doses of estrogen with adequate endometrial protection.
- Asymptomatic except for GSM

<u>Options: Hormone therapy until 51</u>

Ex/ td estradiol patch 0.1 mg+OMP 200 mg/day or MPA 10 mg/day for 12 days/month

Ex/ Femring q 3 months (0.1mg)+OMP 200 mg/day or MPA 10 mg/day for 12 days/month

Ex/ Oral Estradiol 2 mg/day + OMP 200 mg/day for 12 days/mo

Ex/ OCP (EE 20 or 30 mcg/progestin pill; cyclic or continuous ; better to have cyclic regimen-easier to recognized the 5-10% chance for spontaneous pregnancy

(recent evidence demonstrated that 0.1 mg patch plus cyclic MPA was superior to a 30 mcg OCP in improving BMD in women with POI)

* What if she was 38 now, and she had POI at 28??

Case #15 POI Hx; Breastfeeding and 42 y.o.

Case: POI age 33; IVF at 41-42; exclusive breastfeeding for 2 months

History HRT or OCPs age 33 until IVF; had 2 year break and was miserable with severe VMS, joint pains and dyspareunia

No VMS or joint pain during IVF and pregnancy, but now back; does not know about dyspareunia because she has not yet been sexually active post delivery

HRT:

- Recommendation is to wait until breastfeeding well–established (6-8 weeks)
- AAP: maternal medication usually compatible with breastfeeding
  - Minimal transfer to infant, minimal effect on infant

RX=· Transdermal estradiol or combo patch: no effect on milk supply, no adverse effects in infants, does not increase E2 or E3 in infants

Progestogens – transdermal in CombiPatch, IUD, oral

- Using progesterone-releasing IUD- No impact on supply, no difference in infant's growth or development
- Tx plan: estradiol patch 0.025 mg biw (avoided creams due to touching baby) + OMP 100 mg/day

Resources

- Women's Encyclopedia of Natural Medicine, 2008, second edition
- www.drtorihudson.com
- www.awomanstime.com
- www.instituteofwomenshealth.com
- www.naturopathicresidency.org
- Women's Health Updates -Townsend Letter