Menopause
A Review of Systemic Impact and Current Treatment Guidelines

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Learning Objectives

- Explain the biological, physiological, and psychological impact of menopause
- Review current guidelines for hormone replacement therapy
- Discuss non hormonal alternatives to menopausal associated conditions

Before Menopause (peri-menopausal)

- The months/years leading up to menopause
- Common symptoms:
  - Irregularity in menstrual cycles
  - Hot flashes/night sweats may start
  - Changes in mood, sleep, concentration
  - Vaginal dryness
  - Slowing of metabolism, weight gain

Menopause (Meno“stop”)

- Defined after the absence of a menstrual cycle for 12+ months OR lab values consistent with menopause (FSH typically >30 and estradiol typically <30)
- Ovaries are no longer producing estrogen and progesterone
  - However, estrogen is still produced and metabolized in estrogen-sensitive organs (i.e. adipose tissue) although at significantly lower levels (genetically driven)
  - Testosterone still produced by the adrenal glands
- Impacts multiple biological, physiological, and psychological functions
- Significant shift in overall quality of life

Systemic Impacts

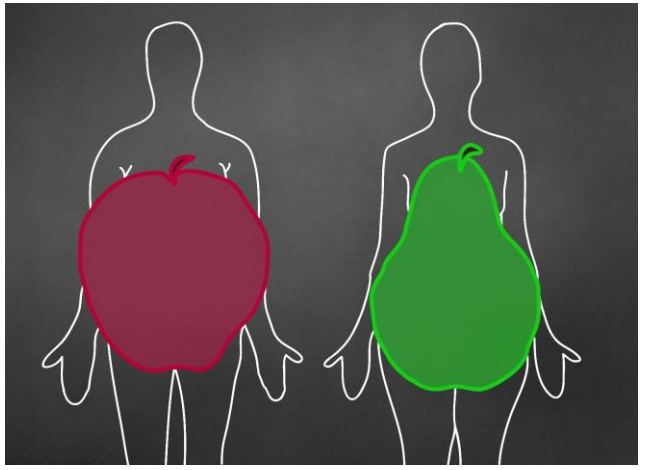
- Cardiovascular Disease
- Metabolic Changes
- Osteoporosis
- Dermal Changes
- Genitourinary Syndrome of Menopause (GSM)
- Cognitive Decline
- Vasomotor Symptoms

Cardiovascular – Shift in Risk after Menopause

- **Cardiovascular disease (CVD) is the leading cause of death and disability in postmenopausal women older than 50 years**[1]
- Rapid increase in prevalence of CVD is seen at the onset of menopause. With continuation of increase through the post-menopausal period
- The complex effects of hormones on the cardiovascular system result in different presentations of coronary heart disease in women:
  - Higher incidence of angina
  - Lower burden of obstructive coronary artery disease (CAD) on angiography
  - Poorer prognosis compared with men
  - More likely to develop heart failure with preserved ejection fraction[2]

1. Health Maintenance in Postmenopausal Women. *Am Fam Physician.* 2017 May 1;95(9):561-570.
2. Garcia M, Miller VM, Gulati M, et al. Focused cardiovascular care for women: the need and role in clinical practice. *Mayo Clin Proc*. 2016;91(2):226–240.

Metabolic – Pear to Apple



- Shifts in hormones appear to accelerate fat accumulation, which appears to accumulate disproportionately in the abdominal area
- This shift is associated with increased insulin resistance and dyslipidemia
- In Women's Health Initiative (WHI) Trials - hormone therapy significantly reduced the diagnosis of new-onset type 2 DM, but it is not FDA approved for this purpose
- Hormone therapy may help attenuate abdominal adipose accumulation and the weight gains that are often associated with the menopause transition

Menopause: *The Journal of The North American Menopause Society.* 2017 Jul; Vol. 24, No. 7, pp. 728-753.

Osteoporosis

- As defined by the National Osteoporosis Foundation: chronic, progressive disease characterized by low bone mass, microarchitecture deterioration of bone tissue, bone fragility, and a consequent increase in fracture risk
- High Prevalence: approx. 50% of white women will have an osteoporotic fracture in their lifetime
- Consequences
  - Disability – 40% regain pre-fracture independence
  - Mortality – 10-20% increased mortality at 1 year
  - Longterm care – 20% of patients with a fracture require assisted care
  - Expensive! – projected to cost $25 billion by 2025
- Risks after menopause: lack of estrogen blockade on receptors allows for osteoclast-driven bone resorption and accelerated rate of bone remodeling

Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2014.

Dermal Changes

- With menopause – skin integrity is impacted
  - Decrease in elasticity
  - Thinning of dermal layers
  - Poor wound healing

- Estrogen therapy (ET) may benefit wound healing through modifying inflammation, stimulating granulation tissue formation, and accelerating re-epithelialization. In studies, ET increased epidermal and dermal thickness, increased collagen and elastin content, and improved skin moisture, with fewer wrinkles[1]

1. Emmerson E, Hardman MJ. The role of estrogen deficiency in skin ageing and wound healing. *Biogerontology* 2012;13:3-20.

Genitourinary Syndrome of Menopause (GSM)

- Symptoms
  - Genital dryness, burning, and irritation
  - Sexual symptoms of diminished lubrication and pain
  - Urinary symptoms of urgency, dysuria, and recurrent urinary tract infections (UTIs)
- Consequence of postmenopausal estrogen deficiency
  - Changes to the labia, vagina, urethra, and bladder
  - Atrophic vulvovaginitis

Cognitive Impact
"I'm losing my mind!"

- Women experience varying degrees of cognitive impact
  - Mood changes (depression, anxiety)
  - Irritability
  - Sleep disruption
  - Lack of focus/concentration
- Dementia?
  - Inconclusive evidence when looking at affects of hormone replacement therapy (HRT) on developing dementia/Alzheimer's with some evidence of worsening if HRT initiated later in life

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Hot Flashes
"Do these ever go away?"

- What are hot flashes?
  - Due to thermoregulatory dysfunction
  - Sensations of heat, sweating, flushing, anxiety, or chills lasting for 1-5 minutes
- Affects sleep, increased irritability, lack of concentration, and overall impacts quality of life
- Lasts longer than we initially thought – median of 7.4 years[1]
  - Asian women 5 years
  - White women 7 years
  - Hispanic women 9 years
  - Black women 10 years

1. Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med* 2015;175:531-9.

Case Study - Janet

- 52-year-old black female; last menstrual period was at 50
  - Trying to “tough it out” but hot flashes are waking her up multiple times each night
  - Missing deadlines at work because she’s tired and can’t concentrate and is gaining weight
  - History of hypertension but is well controlled on medication
  - Hysterectomy at age 41 due to fibroids and heavy periods but kept her ovaries. She is wondering if she should take hormones but is afraid of getting cancer . . .

What would you recommend for Janet?

Hormones help, but are they safe?

Hormones Help…

- Hot flashes
- Sleep
- Mood
- Protect bones
- Genitourinary issues
- Metabolically

But . . . . Are they safe? . . . .

Hormones “Yea or Ney”?

- For years it was “observed” that post menopausal hormone replacement therapy could provide protection from cardiovascular disease and dementia
- The 2002 Women’s Health Initiative (WHI) – post menopausal women ages 50-79
  - 16,608 women with intact uterus randomized to receive Conjugated Equine Estrogen (CEE) (0.625mg) combined with MPA (2.5mg) or placebo
  - 10,739 women s/p hysterectomy randomized to receive CEE (0.625mg) alone or placebo
  - Primary efficacy and safety endpoints: CHD (coronary heart disease) and invasive breast cancer
  - Global index: CVA, PE, CRC, endometrial CA, hip fracture, deaths

CVA=cerebrovascular accident/stroke; PE=pulmonary embolism; CRC=colorectal cancer; CA=cancer

Design of the Women’s Health Initiative clinical trial and observational study. The Women’s Health Initiative Study Group. *Control Clin Trials*. 1998;19(1):61–109.

WHI Findings

- Study was stopped early due to evidence of increased risk – outweighing benefits
  - CEE/MPA arm stopped at 5.9 years (median)
    - Risks: CHD increased in treatment group (hazard ration HR of 1.18), also increased risk of invasive breast CA, CVA, PE and global index. Increased dementia in women > 65
    - Benefits: decreased hip fracture, improvement of vasomotor symptoms, reduced diabetes
    - Post intervention most risks/benefits dissipated except some persistence of breast CA risk
  - CEE arm stopped at 7.2 years (median)
    - More balanced re CHD risk (hazard ration HR of 0.94)
    - Risks CVA, venous thrombosis
    - Benefits: decreased hip fracture, reduced diabetes
    - Post intervention: decrease in breast CA risk
  - Neither regimen affected all cause mortality, mixed results on quality of life
  - Were variations of risks based on age: 50-59 more favorable for all cause mortality, MI, global index but not for CVA and VTE (venous thromboembolism)
  - Cumulative f/u of 13 years (September 30, 2010)

Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321–33.
Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291(14):1701–12.

Additional Information re: CHD

- The impact of hormone therapy on CHD may vary depending on the woman's age at start of treatment and/or how many years she has been in menopause
- Some observational data suggest a reduced risk of CHD in women who start therapy when <60 years old and/or who are within 10 years of menopause
- In women who start therapy >10 years from menopause onset, and even more so if >20 years, there is potential for increased risk of CHD
- In WHI both CEE alone and CEE/MPA increased risk of CHD, with potentially greater risk with CEE/MPA

Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 2013;310:1353-1368.

So What Do We Do Now?

- Hormone therapy is approved by FDA for four indications:
  1. Symptomatic vasomotor symptoms
  2. Prevention of bone loss
  3. Hypoestrogenism (such as premature ovarian failure, surgical menopause)
  4. Genitourinary symptoms
- Recommendation – lowest therapeutic dose to effectively treat the indicated condition for the shortest period of time
- Benefits may outweigh risks when initiated in recently menopausal patients <60 years old

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Goals of Treatment – The 4 "I"s

- **Identify** if a woman is experiencing conditions related to estrogen deficiency
- **Individualize** therapy – adjust dose to obtain clinical efficacy and maximize safety, choosing method of delivery tailored to patient
- **Initiation** of therapy (timing from start of menopause to start of therapy) to optimize its efficacy and minimize adverse events/risks
- **Inquire** – check-in with patient annually regarding their therapy – Is it still effective? Is it still needed? Is it still safe to take?

Contraindications to using HRT

- Active liver disease
- Active or recent arterial thromboembolic disease (i.e. angina, MI)
- Current, past, or suspected breast cancer
- Known hypersensitivity to HRT
- Known or suspected estrogen-sensitive malignant condition
- Porphyria cutanea tarda (absolute contraindication)
- Previous idiopathic or current VTE (DVT, PE)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Untreated hypertension

Am Fam Physician. 2012 Nov 1;86(9):864-868.

Hormone Replacement Options

Estrogen Only	Route	Formulations
Estradiol (multiple brand formulations)*	Transdermal patch, injection, gel, vaginal cream, skin cream, vaginal insert, vaginal ring, oral tablet, transdermal skin spray, vaginal tablet, injection	Micronized estradiol – 17β Estradiol acetate Estradiol Valerate
Conjugated Estrogen (Premarin)	Oral pill, vaginal cream, injection	
Estropipate (Ogen, Ortho-Est)	Oral pill, vaginal cream	
Esterified Estrogen (Menest)	Oral pill	
Synthetic Conjugated Estrogen (Cenestin, Enjuvia)	Oral pill	
Ospemifene (Osphena) **(Tissue selective estrogen agonist/antagonist)**	Oral pill (FDA approved for dyspareunia)	

*https://www.fda.gov/consumers/free-publications-women/menopause-medicines-help-you Accessed April 22, 2021

Hormone Replacement Options

Progesterone Only	Route	Formulations
Micronized Progesterone (Prometrium)	Oral pill	
Medroxyprogesterone acetate (Provera)	Oral pill	

Other options (not FDA approved) – may include progesterone containing IUDs or topical progesterone creams

https://www.fda.gov/consumers/free-publications-women/menopause-medicines-help-you Accessed April 22, 2021

Hormone Replacement Options

Combination Estrogen and Progesterone	Route
Estradiol/norethindrone acetate (Activella, Combipatch)	Oral pill Transdermal patch
Estradiol/drospiernone (Angeliq)	Oral pill
Estradiol/levonrgestrel (Climera Pro)	Transdermal patch
Norethindrone acetate/ethinyl estradiol (Femhrt)	Oral pill
Estradiol/norgestimate (Prefest)	Oral pill
Conjugated estrogen/medroxyprogesterone (Prempro)	Oral pill
Conjugated estrogen/bazedoxifene (Duavee) **(Combination Estrogen/Selective Estrogen Receptor Modulator)**	Oral tablet

https://www.fda.gov/consumers/free-publications-women/menopause-medicines-help-you Accessed April 22, 2021

Conjugated Estrogen vs Estradiol

- The different formulations vary in content, pharmacokinetics, and pharmacodynamics
  - Conjugated Equine Estrogens (CEE) “partially natural”
  - Micronized 17beta Estradiol (E2) “completely natural”
  - Ethinyl Estradiol (EE) “synthetic”
- The variations are further affected by dosage and route of administration – although the full impact is not clearly understood
- Serum lab testing – not reliable – does not measure all active/bioavailable components, levels vary over time, does not correlate with response
- Base adjustment of dose, type, delivery method based on response

MedGenMed. 2006; 8(1): 85. Published online 2006 Mar 28.

Conjugated Estrogens/Bazedoxifene

- FDA approved for the treatment of moderate to severe vasomotor symptoms associated with menopause and prevention of postmenopausal osteoporosis
- Dosing: 0.45mg/20mg tablet taken once daily with or without food
- Bazedoxifene is a selective estrogen receptor modulator:
  - Stimulates estrogen receptors in bone
  - Antagonistic effects in the breast and uterus
- In clinical trials showed statistically significant improvements in:
  - Sexual functioning
  - Menopause-related quality of life
  - Sleep quality
  - Maintenance or slight increase in bone mineral density in lumbar spine and hip – effect on vertebral, hip, or overall fracture rate is unknown

Kristina Johnson, MD, and Fern Hauck, MD, MS, University of Virginia Depart of Fam Med, Charlottesville, Virginia *Am Fam Physicians*. 2016 Feb 15;93(4):307-314.

CE/Bazedoxifene: Safety

- When compared to CE/MPA formulation CE/Bazedoxifene results in less vaginal bleeding
- Boxed warning:
  - Increased dementia in women >65
  - Endometrial CA
  - CVA
  - DVT (Deep Vein Thrombosis)
- Should not be used in the following patients:
  - Abnormal uterine bleeding
  - Breast CA or other estrogen-dependent neoplasia
  - Venous or arterial thromboembolism
  - Liver disease
  - Thromboembolic disorders

Kristina Johnson, MD, and Fern Hauck, MD, MS, University of Virginia Depart of Fam Med, Charlottesville, Virginia *Am Fam Physicians*. 2016 Feb 15;93(4):307-314.

Back to Case Study - Janet

- 52-year-old black female whose last menstrual period was at age 50
  - Hot flashes are waking her up multiple times each night
  - Missing deadlines at work because she is tired and can't concentrate
  - Gaining weight
  - Controlled hypertension
  - No uterus
  - Worried about cancer risk

"I heard natural hormones were safer"

Compounded Bio-identical Hormones

- Compounded formulation claim to be identical in structure to human hormones (in many cases this has not been biochemically sustained)
- Compounded bioidentical HT presents safety concerns:
  - Minimal government regulation and monitoring
  - Overdosing or underdosing
  - Presence of impurities or lack of sterility
  - Lack of scientific efficacy and safety data (can’t say better or worse)
  - Lack of a label outlining risks

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New Case Study – Mary

- 60-year-old Asian, postmenopausal woman
  - Been on combined estrogen/progesterone HRT 0.45mg/1.5mg daily since she started menopause 6 years ago
  - Recently diagnosed with stage II ER/PR+ invasive breast cancer
  - She is coming to you to discuss what she can expect when stopping hormones and options to keep her feeling “normal” . . .

Non-Hormonal Treatment for Vasomotor Symptoms of Menopause[1]

Treatment	Route	Effective dosage
Alpha-adrenergic blocking agents – Clonidine (Catapres)	Oral daily tablet Transdermal weekly patch	0.1 mg per day
Gabapentin (Neurontin)	Oral tablet	900mg/day in divided doses
Lifestyle modifications	Relaxation: yoga, meditation Fans/AC Light/loose clothing	
Pollen Extract (Relizen, Femal)[2]	Oral tablet	2 tablets daily (minimum of 2-3 months to start seeing benefit)
Phytoestrogens - **Black Cohash** - **Soy**	Oral capsule Various sources	40mg daily for black cohash (avoid in patients with estrogen sensitive neoplasia)
SSRIs - **Fluoxetine** (Prozac) - **Paroxetine** (Brisdelle, Paxil)	Oral tablet/Capsule daily	- 20mg - 7.5 (Brisdelle) - 12.5-25mg (Paxil CR) or 20mg (Paxil)
SNRIs - **Venlafaxine** (Effexor)	Oral tablet/Capsule	37.5-75mg XR formulation daily

1. *Am Fam Physician*. 2012 Nov 1;86(9):864-868. 2. Hellstrom AC, Muntzing J. The pollen extract Femal—a nonestrogenic alternative to hormone therapy in women with menopausal symptoms. *Menopause.* Jul 2012;19(7):825-829.

Complimentary & Alternative Medicine (CAM) to treat Menopause

- 51% of women report using CAM
- 60% of these women report perceived benefit
- Evidence is mixed with regards to safety and efficacy
- Patients often don’t openly discuss with providers
- Important we address integrative approaches to reduce undertreatment and risk

Johnson A, Roberts L, Elkins G. Complementary and Alternative Medicine for Menopause. *J Evid Based Integr Med*. 2019;24:2515690X19829380. doi:10.1177/2515690X19829380

Mind-Body Practices

- **Hypnosis for Hot Flashes**: RCT showed equally as effective when compared to venlafaxine 75mg (50% reduction in vasomotor symptoms (VMS) compared to 25% placebo)
  - Recommended by the North American Menopause Society (NAMS) for the treatment of menopausal symptoms and poses little risk
- **Cognitive Behavioral Therapy (CBT):** when compared to placebo – reduction in VMS interference but not in frequency
  - Recommended by NAMS for reduction of bothersome symptoms but not for frequency
- **Relaxation & Biofeedback**: conflicting evidence – may provide some benefit but more evidence is needed to draw conclusions
- **Meditation**: Mindfulness-Based Stress Reduction (MBSR) – variety of exercises including meditation/yoga etc – low risk, may reduce stress/anxiety and improve sleep but no evidence in reduction in VMS
- **Aromatherapy**: may be helpful when combined with massage (stress relief) but no evidence of benefit alone

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Natural Products
Herbals, Vitamins, Dietary Supplements

- **Black Cohosh (*Cimicifuga racemosa*)** side effects of black cohosh may include: gastrointestinal problems, rash, and acute hepatitis
- **Wild Yam (*Diascorea*)**
- **Dong Quai (*Angelica sinensis*)** safety concerns exist regarding *A sinensis*, including interactions with other medications and herbs, photosensitization, anticoagulation, and possible carcinogenicity
- **Maca (*Lepidium meyenii*)**
- **Pollen Extract**
- **Evening Primrose Oil (*Oenothera biennis*)**
- **Phytoestrogens**
- **Vitamin E**

Consensus: more studies needed to draw conclusions

Johnson A, Roberts L, Elkins G. Complementary and Alternative Medicine for Menopause. *J Evid Based Integr Med*. 2019;24:2515690X19829380. doi:10.1177/2515690X19829380

Whole System Approach (Mind-Body Practices + Natural Products)

- Traditional Chinese Medicine
- Reflexology
- Acupuncture
- Homeopathy

Consensus: more studies needed to draw conclusions

Johnson A, Roberts L, Elkins G. Complementary and Alternative Medicine for Menopause. *J Evid Based Integr Med*. 2019;24:2515690X19829380. doi:10.1177/2515690X19829380

Back to Mary

- 60-year-old, Asian female
- Menopausal x 6 years
- On HRT – recently diagnosed with ER/PR+ breast CA
- What do we expect? What can we offer?

Considerations:

- Age
- Race
- Treatment for Cancer?
- Other disease states (bones?)

Case Study – Beth (Libido)
Don't they make Viagra for women?

- 50-year-old white female experiencing irregular menstrual cycles for past 7 months
  - Started noticing periodic hot flashes and night sweats but tolerable
  - More concerning is it's become painful when she has intercourse and has had 3 UTIs in the past 6 months
  - Just doesn't feel like having sex anymore – not interested
  - Happily married for 26 years and wants to get her "mojo" back!

GSM – Recap From Earlier

- Symptoms
  - Genital dryness, burning, and irritation
  - Sexual symptoms of diminished lubrication and pain
  - Urinary symptoms of urgency, dysuria, and recurrent urinary tract infections (UTIs)
- Consequence of postmenopausal estrogen deficiency
  - Changes to the labia, vagina, urethra, and bladder
  - Atrophic vulvovaginitis

What can we do to help??

Options for GSM Treatment

- Topical Estrogen – vaginal cream, tablet
- Ospemifene (Osphena) – oral tablet
- Prasterone (DHEA) (Intrarosa) – 6.5mg intravaginal insert QHS
- Hyaluronic Acid (Revaree) – vaginal insert 2-3 nights/week
- Over the counter lubricants
- Pelvic physical therapy
- Laser therapy
- Radiofrequency therapy

Vaginal Estrogen Treatment

Treatment	Route	Effective dosage
Vaginal Cream - **Estradiol** (Estrace) - **Estropipate** (Ogen) - **Conjugated estrogen** (Premarin)	Intravaginally with applicator frequency varies – often higher dose nightly initially then tapering down to lower dose 2-3 nights per week for maintenance	- 0.1mg/g (1-4 grams) - 1.5mg/g (2-4 grams) - 0.625mg/g (0.5-2 grams)
Vaginal Ring - **Estradiol** (Estring) - **Estradiol acetate** (Femring)	Inserted Vaginally – inserted 1 ring every 90 days	- 2mg/day - 0.05mg/day or 0.1mg/day
Vaginal Tablet - **Estradiol** (Vagifem)	Tablet inserted nightly for 2 weeks then decrease to maintenance dose of 2 nights/week	10mcg/tablet

Ospemifene 60mg Oral Tablet Daily

- An estrogen agonist/antagonist FDA approved in 2013 for:
  - The treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause
  - The treatment of moderate to severe vaginal dryness, a symptom of vulvar and vaginal atrophy, due to menopause
- Adverse Reactions: hot flush, vaginal discharge, muscle spasms, headache, hyperhidrosis, vaginal hemorrhage, night sweats
- Drug-drug interaction
  - Fluconazole (increase serum concentration of ospemifene)
  - Rifampin (decrease serum concentration of ospemifene)
- Black box warning
  - Endometrial cancer (increased risk)
  - Cardiovascular Disorder (CVA/DVT increased risk)

Osphena prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203505s015lbl.pdf

Prasterone 6.5mg (DHEA)

- A steroid indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause
- FDA approved 2019
- Intravaginal insert – dosed nightly at bedtime
- Contraindicated in undiagnosed vaginal bleeding
- Caution in patients with history of breast cancer (DHEA converted to estrogen in the body)
- Side effect – vaginal discharge

Intrarosa prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208470s000lbl.pdf

Hyaluronic Acid Sodium Salt 0.25%

- Through the creation of new blood vessels, hyaluronic acid can improve the vaginal epithelium's ability to repair itself and reverse vaginal atrophy without exhibiting any hormonal effects[1]
- In a randomized, controlled, 30-day head-to-head clinical trial of 144 women: Hyaluronic acid demonstrated comparable efficacy to topical estrogen in relieving vaginal atrophy[2]
  - At 9 days and at 30 days hyaluronic acid significantly improved multiple symptoms of vaginal atrophy ($P<0.05$)
  - No significant difference versus estrogen cream ($P>0.05$)
- Vaginal Suppository – inserted at bedtime 2-3 nights per week

1. Liu SB, Liu SL, Gan XL, et al. *Gynecol Endocrinol*. 2015;31:208-213.
2. Chen J, et al. *J Sex Med*. 2013;10:1575-1584.

Procedural Options – "Vaginal Rejuvenation"

- Uses energy to heat the vaginal tissue
  - Stimulates collagen formation
  - Improve circulation through stimulation of new blood vessel formation
  - Improve tightness
  - Improve lubrication
- Not typically covered by insurance – treatments can be expensive
  - In Orange County, CA ranges from $1800-$2500 for series of 3 treatments
- CO_2 laser treatment: heats up the superficial tissue resulting in collagen production in deeper layers
  - MonaLisa Touch®, FemTouch™ and FemiLift
- Radiofrequency (RF): Electromagnetic waves are used in RF devices
  - Geneveve by Viveve and ThermiVa

Libido – Physiological Component

- Physiologic
  - The female sexual response involves the production of Endothelial Nitric Oxide Synthase (eNOS)[1]
  - eNOS converts arginine and citrulline into nitric oxide (NO)
  - NO increases genital tissue circulation
  - eNOS decreases with age and hormonal changes[2,3]
  - Rose hips extract, a potent antioxidant, has been shown to significantly reduce free radicals and improve oxidative stress after 8 weeks, supporting overall sexual function.[1,4]
  - Replacing estrogen seems to have little effect on sexual function in menopausal women (small improvement with transdermal formulation)[5]

1. Stanislavov R and Rohdewald P. *J Women's Health Care*. 2014;3:1-6. 8-week, randomized, double-blind, placebo-controlled study conducted in 80 women ages 40-50. 2. Musicki et al. *J Sex Med.* 2009; 6:247-253. 3. Matsushita et al. *Circ Res*. 2001; 89:793-8. 4. Bottari A, et al. *Minerva Genecol*. 2013;65:435-444. 8-week, active-controlled lifestyle study in 100 premenopausal women ages 37- 45. 5. *Am Fam Physicians*. 2018 Mar 15;97(6):408.

Female "Viagra"?

- "Viagra" (sildenafil) and similar medications work in men to increase penile blood flow which enhances erectile function – does not affect "sex drive" (i.e., libido)
- FDA approved medications for PREMENOPAUSAL women with HSDD (hypoactive sexual desire disorder)
  - Bremelanotide (Vyleesi): exact MOA unknown, injectable[1]
    - Activates melanocortin receptors
  - Flibanserin (Addyi): exact MOA unknown, oral tablet[2]
    - In vitro: high agonist activity at 5-HT1A and antagonist activity at 5-HT2A. Moderate antagonist activities at the 5-HT2B, 5-HT2C, and dopamine D4 receptors

[1]Vylessi 2021 Palatin Technologies, Inc.- prescribing information
[2]Addyi 2020 Sprout Pharmaceuticals, Inc. US - prescribing information

Ristela

- In three randomized controlled trials across a total of 236 women: Ristela showed statistical improvement of patients' overall Female Sexual Function Index scores at 4 weeks and 8 weeks ($P<0.05$)[1,2,3]
- Ristella contains: Pycnogenol (pine bark extract) shown to increase eNOS; L-Arginine, L-Citrulline, and Rose Hips extract
- Dosing: 2 tablets once daily
- Effective pre, peri, and postmenopausally[1,2,3]
- In postmenopausal women: 59% Improvement over one month 61% Improvement over two months[3]

1. Bottari A, et al. *Minerva Genecol*. 2013;65:435-444. 8-week, active-controlled lifestyle study in 100 premenopausal women ages 37- 45.
2. Stanislavov R and Rohdewald P. *J Women's Health Care*. 2014;3:1-6. 8-week, randomized, double-blind, placebo-controlled study conducted in 80 women ages 40-50.
3. Bottari A, et al. *Panminerva Med*. 2012;54:3-9. 8-week, randomized, single-blind, placebo-controlled study in 83 postmenopausal women ages 45-55.

Back to Beth

- 50 years old
- Perimenopausal
- Vasomotor symptoms tolerable
- Biggest concerns:
  - Dyspareunia
  - UTIs
  - No Libido

Suggestions??

Summary of Case Studies

- Janet
  - Good candidate for low dose, short term use of approved HRT for her primary complaint of vasomotor symptoms

- Mary
  - Pursue non hormonal options for appropriate conditions
    - Bones
    - Mood/sleep

- Beth
  - Address both physiologic and psychologic aspects of “libido” in the postmenopausal woman

Summary

- Menopause occurs when the ovaries cease to produce estrogen and progesterone
- Impacts multiple biological, physiological, psychological functions
- Can significantly impact a woman's quality of life
- Hormone therapy is approved by FDA for four indications:
  1. Symptomatic vasomotor symptoms
  2. Prevention of bone loss
  3. Hypoestrogenism (such as premature ovarian failure, surgical menopause)
  4. Genitourinary symptoms

Summary *cont.*

- Recommendation – lowest therapeutic dose to effectively treat the indicated condition for the shortest period of time
- Benefits may outweigh risks when initiated in recently menopausal patients <60 years old
- There are effective non-hormonal treatment options for those women who are unable to choose not to take hormones
- Therapy should be individualized based on symptoms, risks, desire to treat