Embrace the Change

Treatment options for perimenopause and menopause

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Disclosures

- None

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Symptoms and Signs during Perimenopause

Sleep disturbances

Altered mood including depression and anxiety

Brain Fog

Weight gain

Contraception/Medical issues

Hot flashes

Pain with sex

Low libido

Irregular bleeding

Joint pain

Hair loss/skin changes/dry eyes

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Objectives

1. Identify the stages for menopause in order to understand which treatment options work best in each stage.
2. Identify the role of contraception in the perimenopausal stage.
3. Review treatment options for vasomotor symptoms.
4. Review common treatments for sexual dysfunction symptoms

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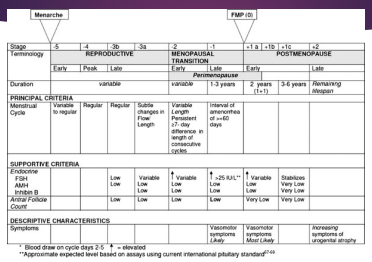
Stages of Reproductive Aging: STRAW STUDY



Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
	Perimenopause									
Duration	variable				variable	1-3 years	2 years (1+1)		3-6 years	Remaining lifespan
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow Length	Variable Length Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of ≥=60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			Low Low	Variable Low Low	↑ Variable Low Low	↑ >25 IU/L** Low Low	↑ Variable Low Low	Stabilizes Very Low Very Low		
Antral Follicle Count			Low	Low	Low	Low	Very Low	Very Low		
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms Likely	Vasomotor symptoms Most Likely			Increasing symptoms of urogenital atrophy

* Blood draw on cycle days 2-5 ↑ = elevated
**Approximate expected level based on assays using current international pituitary standard[249]

Menopause 19(4):387-395, April 2012.

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Menopause : 12 months without a period

- Median age 51-52
- Late after 55
- Early before 45
- Prior to age 40 is Premature Ovarian Insufficiency

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Stages of Reproductive Aging

-3b/-3a
Late Reproductive:
Cycles regular/irregular
Normal to variable FSH

➡

-2
Early Peri:
Cycles variable
Variable FSH

Median age 47 "Hormonal Magnification"

➡

-1
Late Peri :
Cycles >=60 days
FSH high

Median age 49 "Hormonal Deficiency"

➡

0
FMP

Median age 52

➡

+1a/+1b
Menopause:
Menses done
FSH high

Menopause 19(4):387-395, April 2012

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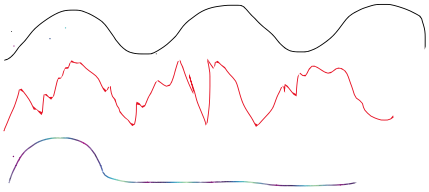
Hormonal Patterns



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Contraception

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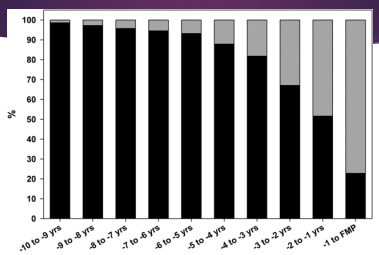
Ovulatory Cycles



From: Menstrual Cycle Hormone Changes in Women Traversing Menopause: Study of Women's Health Across the Nation J Clin Endocrinol Metab. 2017;102(7):2218-2229. doi:10.1210/jc.2016-4017 J Clin Endocrinol Metab | Copyright © 2017 Endocrine Society

ELA: evidence of luteal activity

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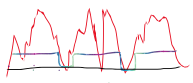
COMBINED ORAL CONTRACEPTION (COC): PERIMENOPAUSE TREATMENT

- CONTRACEPTION
- BLEEDING
- PMS/mood
- Menstrual Headaches
- HOT FLASHES*



*10% of women can still have hot flashes with ethinyl estradiol
Can consider COC with E4 or HT with Progesterone contraception

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When do you stop COC?

The Menopause Society | Practice Pearl

Contraception in Perimenopause

Released January 16, 2025

- Caution is recommended given age >45 yrs has higher risk of thromboembolism
- COC increases risk of MI and stroke vs nonusers but no difference with age
- **Menopause Society:" Assuming that there are no contraindications/comorbidities, women can remain on a low-dose COC including the vaginal ring and contraceptive patch, until age 55."** Balance risk vs potential benefit
- 85% of women are menopausal by age 52, 90% by 55
- No Data to support that lower dose COC have less risk of thromboembolism: consider 10 or 20mg pill

Lidegaard, Thrombotic stroke and MI associated with hormonal contraception. NEJM 2012; 366:2257-66
McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. Maturitas 1992;14:103-115.
Soltes B. Menopause society: Clinal Pearl: contraception in perimenopause Ja n2025

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Prevalence of Health Problems in Women age 45-54

Hypertension	29.5%
Hyperlipidemia	31.2%
Cigarette smoking and vaping	19.8%
T2DM	12.7%
Migraines with aura	12%

Contraception

Hormonal IUD or Progesterone pill

T x

PLUS ESTROGEN PATCH

Black. HAMS perimenopause 101: Contraception During the Menopause Transition: Choices and Challenges
www.cdc.gov/nchs/fhs/women/fdm. Centers for Disease Control and Prevention 2016.
Allen et al. CMAJ 2015. 187(7): 565-573 Mantha S. BMJ. 2012;345:e4944. CDC morbidity and mortality 2023

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Vasomotor Symptoms

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Vasomotor symptoms

- VMS is an extreme thermoregulatory response that last 1-3 minutes
  - -Sweating
  - -Flushing
  - -increased HR
- Pathophysiology unknown but due to loss of estrogen + endothelial dysfunction of blood vessels
- 75-80% of women will experience VMS with 33% more 10 a day
- Median duration 4-10.2 years;
- Can affect sleep mood and cognitive function
- Risk factors: weight, smokers, race

ACOG PB #141 Management of menopausal symptoms

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Treatment options

Hormones

Perimenopause
-COC
-Estrogen therapy (ET)
-Estrogen +Progesterone therapy (EPT)

Postmenopausal
-ET
-EPT
-E Receptor Agonist/Antagonist

Nonhormonal

Paxil (Brisdelle)
SNRI *
Gabapentin *
Clonidine*
*Oxybutynin**
Neurokinin B Antagonist

Other

Herbals/Supplements *
RCT's show no improvement or conflicting data
-black cohosh, St John's wort, isoflavone,phytoestrogens

Lifestyle changes
Decrease Caffeine & ETOH, weight loss, smoking cessation, Acupuncture, Paced respirations

*not FDA approved

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Hormonal options

- 1970's oral Premarin → endometrial CA
- 1980's add progesterone
- 1990's CVD protection
- 2002 WHI → no CVD protection
- 2020's... here we are now

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WHI 2002: role HT and Coronary Heart Disease (CHD) in postmenopausal women

- Healthy postmenopausal women 50-79
- **MEAN AGE 63**
- Role of HT and CHD
- double blinded RCT : two Hormonal trials
  - -Hysterectomy: conjugated equine estrogen (ET) 0.625mg
  - -Uterus: EPT (estrogen progesterone therapy) with CEE combined with MPA 2.5mg

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Outcomes: WHI

- A total of 335 cases of CHD were included in this final analysis
- **EPT: 2x of DVT, PE and breast cancer after 5 year use (discontinued 5.2 yr)**
- **ET: DVT 3-4X, increased stroke (discontinued 6.8yrs)**
- EPT does not prevent CHD & can increases the risk of CHD among generally healthy postmenopausal women. This treatment **should not be prescribed for the prevention of cardiovascular disease**
- **The WHI was not designed to study the effects of postmenopausal hormone therapy on menopausal symptoms. EXCEEDED AGE OF STARTING HT (MEAN AGE 63)**

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Age and time since menopause onset: *timing hypothesis*

- Stratified to 50-59yrs per 1000 women
  - → fewer deaths
  - → fewer cases of CHD
  - → 5 extra blood clots over 7 years
  - → no difference in stroke
- The effects of HT on CHD may vary depending on a woman's age and time since menopause onset

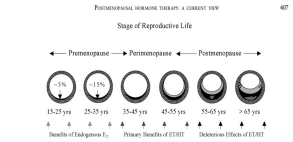

Figure 1. Schematic depiction of the natural history of atherosclerosis among women in the United States. The premenopausal data are based on findings from the Pathologic Determinants of Atherosclerosis in Youth (PDAY) Study (47). The numbers shown in the lumen (~5% and ~15%) refer to the surface of coronary arteries with fatty streaks. The data on older women are autopsy derived characterizations based on McGill and Stern 1979 (43) and Tejada et al. 1998 (44). ET = Estrogen therapy, HT = Hormone therapy.

Boardman H, et al. HT for prevention of CVD in PM. Cohrabne Data Base 2015.
The 2022 hormone therapy position statement of The North American Menopause Society.
Menopause. Mikkola T, Et al. Postmenopausal hormone therapy 2004. Mikkola Te et al. Ann Med2002;34:462-413

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Age and time since menopause onset: *timing hypothesis*

- **Kronos early estrogen Prevention Study (KEEPS)** Millet et al. Menopause 2019
  - -4 yr RCT oral vs patch vs placebo women age 42-58 yrs old
  - -measured carotid intima media thickness & coronary artery calcifications
  - -no adverse effects
  - -there was a trend to reduce coronary artery progression in oral Premarin group
- **Early vs late postmenopausal treatment with estradiol study (ELITE)** Hodis et al. NEJM 2016
  - - 5 year RCT oral vs placebo initiated in **early vs late menopause** women
  - -measure Carotid intima media thickness Q 6 with CT for calcification scores
  - -significantly slower carotid intima media thickness progression in women < 6 years out from menopause
  - -**estradiol therapy suppresses atherosclerosis development when initiated early after menopause**

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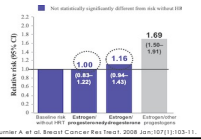
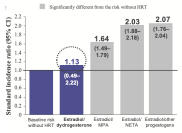
Risk of breast cancer E+P: does the type progesterone matter ?

- French E3N cohort study: different E+P therapies & risk of breast cancer
  - -No difference in route of E for cancer risk
  - -Choice of P is important in breast cancer risk
  - -Dydrogesterone (not available in the us)



Fournier A et al. Breast Cancer Res Treat. 2008 Jan;107(1):103-11.

- Nationwide Finnish Comparative study: cohort study
  - - E2 + progestogen: increase risk at 3 yr
  - -risk is lower sequential progesterone
  - -no difference oral vs transdermal
  - -risk varies by progesterone



Lyytinen H et al. Obst Gyn 2009;113:65–73.

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Differing risks of hormone therapy for women

- Treatment should be individualized using best available evidence to maximize benefits and minimize risks
  - type, dose, duration, route of administration, and timing of initiation
  - HT can be safe when given within 10 years of menopause and age < 60 years old without risk factors

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The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause.*

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Hormone therapy (HT) and vasomotor symptoms

- **Hormone therapy remains the gold standard for relief of vasomotor symptoms (VMS)**
  - Estrogen-alone therapy (ET) is used for symptomatic women after hysterectomy
  - For symptomatic women with a uterus, combination therapy protects against endometrial neoplasia, either with a progestogen or a combination of conjugated equine estrogen and bazedoxifene
  - HT is NOT CONTRACEPTION

The Menopause Society™ Leading the Conversation

The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause.* 2017;24(7):728-753.

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Contraindications

- Abnormal bleeding
  -Heavy bleeding, intermenstrual bleeding, Postcoital bleeding, PMB
- Estrogen sensitive cancers (Endometrial/Breast cancer)
- History of Stroke/MI
- Severe liver disease
- *History of DVT or inherited high risk for DVT**

*Olie V, Plu-Bureau G, Conard J, Horellou MH, Canonico M, Scarabin PY. Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. Menopause. 2011 May;18(5):488-93.

The 2022 hormone therapy position statement of The North American Menopause Society *Menopause*.

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Formulations of Systemic Estrogen HT for VMS
*if has uterus must add progesterone

Oral

Drug	Name	Dose
Conjugated estrogen (CEE)	Premarin	0.3-1.25 mg
Estradiol Estrogen	Menest	0.3-2.5 mg
Synthetic CE	Cenestin	0.3-1.25 mg
17B-estadiol	Estrace	0.3-1.25 mg
Estradiol acetate	Femtrace	0.45-1.8mg
Estropipate	Othro-est	0.625-5mg

Transdermal

Drug	Name	Dose
17-estradiol matrix patch	Alora, Climara, Esclim, Fempatch, menostar, Minivelle, Vivelle	0.014-0.1mg daily or twice a week
17-estradiol gel	Divigel, Estrogel	0.025-1g daily
17-estradoil spray	Evamist	1-3 spray daily
Estradiol acetate ring	Femring	12.4mg or 24.8mg for 90d (release 0.05mg/d or 0.10mg/d)

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Equivalent dose of estrogen

Premature Ovarian Insufficiency

- **CEE: 1.25 mg PO**
- **Estradiol: 2mg PO**
- **Transdermal estradiol 0.1mg**

Peri and early Postmenopausal doses

- **CEE 0.625 mg PO**
- **Estradiol 1mg PO**
- **Transdermal estradiol: 0.05mg**

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Transdermal hormone therapy

- Observational data: transdermal therapy appears to be associated with lower venous thromboembolic & stroke risk
- But the lack of comparative randomized control trial data limits recommendations

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Oral vs Transdermal estrogen

ORAL ESTROGEN

PROS
- Neutral to mild effect on HDL, LDL, cholesterol
- Low cost

CONS
- Risk of thrombosis/stroke
- Increase TG, C-reactive protein
- Decrease libido by increasing SHBG
- Gallstone, pancreatitis

TRANSDERMAL ESTROGEN

PROS
- **Theoretical less risk of dvt/stroke**
- Avoids 1st pass metabolism→ **nonfluctuating serum level**
- Fewer GI adverse effects
- **Less increase in SHBG**
- **Less increase in TG and C-reactive protein**
- More options for tapering

CONS
- Risk of thrombosis/stroke
- **Adhesive residue or risk of spread with gel**
- Less private
- **More costly**

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Progesterone: Endometrial Protection
Continuous =Daily
Cyclic =12 continuous days a month

Drug	Name	Dose	Side Effect
Medroxyprogesterone acetate (MPA)	Provera	2.5mg- 5mg continuous/5mg cyclic	WHI study: breast CA, DVT
Norethindrone acetate (NEA)	Aygestin	0.5-1mg continuous/2.5mg cyclic	Mood, insomnia, Finish study: Breast CA, DVT
Norethindrone	Micronor*	0.35mg continuous*/ 0.7mg cyclic	Mood, acne , irregular bleeding
Micronized progesterone	**Prometrium**	**100mg -200mg continuous/ 200mg cyclic**	**Sleepiness, irregular bleeding**
Drospirenone	Slynd*	4mg/d	Decreased libido
Levonorgestrel	Mirena/Lilleta*	20ug/d	Irregular bleeding

*can be used for contraception

Cockrum et al. Ob&gyn Sept 2022: 140(3):447-487

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Combined Formulations of Systemic Estrogen + Uterine protection for HT

Drug	Name	Dose
CE + MPA	Prempro oral	0.625 +2.5mg to 0.45mg + 1.5mgMPA
CE +NEA	Femhrt oral	2.5u+0.5mg To 5ug +1mg
17B-estradiol +NEA	Activella oral	0.5mg E+1mg
17B-Estradiol +drospirenone	Angelia oral	0.5mg + 0.25mg and 1mg + 0.5mg
CE + Bazedoxifene	Duavee oral	0.45mg CE +20mgBazedoxifene
17B estradiol +NEA	Combipatch	0.05mg +0.1mg and 0.25mg of P Twice a week
17B estradiol +LNG	Climara Pro patch	0.045mg + 0.015mg once week

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Potential Adverse events of EPT or ET

- **Irregular bleeding** (consider dose changes, or progesterone)
- **Mood changes** (consider switching progesterone)
- Breast tenderness
- Nausea
- Abdominal bloating
- Fluid retention
- Headache
- Gallstones

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Calculate ASCVD Risk for HT START

ASCVD risk < 5% and 1 or less risk factor
ORAL OR TRANSDERMAL

ASCVD risk 5-10% or > 2 risk factors
TRANSDERMAL

ASCVD risk > 10%

ASCVD Risk Factors

- •Diabetes
- • Hyperlipidemia
- • Cigarette smoking
- • Hypertension
- • History of preeclampsia
- • Family history of premature high-risk CVD in first-degree relative (men <55 or women <65 years)
- • Coronary calcification (CAC 1-99 moderate risk; CAC > 100 , High risk)
- •Obesity (BMI) > 30
- •Physical inactivity
- •autoimmune collagen-vascular disease (e.g. Lupus or Rheumatoid Arthritis)

Stuenkel C, Et al. Tx of symptoms of the menopause: practice guideline. J Clin Endo Metab 2015 Nov:100 (11)3975-4011

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HOW TO START:

Menopause Stage/Age	With uterus	Without uterus
40-45 Premature/early menopause *	-Estradiol patch 0.1mg/24 hr or oral estradiol 2mg daily with IUD, POP, or cyclic 200mg prometrium or 5mg MPA	Estradiol patch 0.1 mg patch or oral 2mg daily
Late 40-early 50's Perimenopause*	-Estradiol patch 0.05mg /24hr or oral estradiol 1mg daily with IUD, POP, cyclic or continuous prometrium	Estradiol patch 0.05 mg patch or oral 1mg daily
Mid to late menopause 55 to 60	Estradiol patch 0.025 to 0.0375mg/24hr or oral estradiol 0.5mg daily with continuous prometrium 100mg daily	Estradiol patch 0.025 -0.0375mg or oral estradiol 0.5mg

- *Is contraception needed? *Is heavy bleeding a concern?

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Stopping HT

- HT does not have to be discontinued at 60 or 65
- Long term use may be considered in healthy women at low risk CVD & breast cancer risk **with persistent VMS for whom other therapies are not appropriate**
- Longer durations beyond age 60 should include periodic reevaluation of comorbidities with consideration of periodic trials of lowering/discontinuing
- Shared decision reviewing risks should be made
- Use the appropriate effective dose for time needed

Carol found her own way of coping with the hot flushes

The 2022 hormone therapy position statement of The North American Menopause Society :*Menopause.*

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Concerns about compounded bioidentical hormone therapy

- Unique concerns about safety surround use of compounded bioidentical hormone therapy
  - Lack of regulation and monitoring
  - Possibility of overdosing or under dosing
  - Lack of scientific efficacy and safety data
  - Lack of a label outlining risks
- No evidence to support use of routine serum or salivary hormone testing

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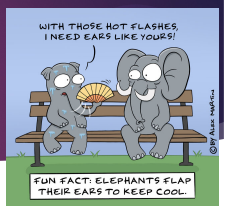
Non-hormonal options



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Brisdelle for hot flashes: Paroxetine Mesylate 7.5 mg

- FDA approved medication
- 6-8 weeks to see results
- RCT Simon JA et al Menopause 2013;20 (10): 1027-1035
  - -women with median 10 hot flushes per day.
  - -Paroxetine mesylate reduction 5.6 hot flushe
    No impact on weight or libido
- avoid use in patients on Tamoxifen

Simon JA et al Menopause 2013;20 (10): 1027-1035

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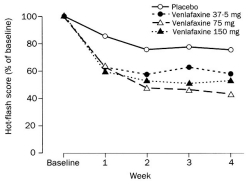
Off Label use SSRI/SNRI for hot flashes

Side effects dry mouth, constipation, loss of libido, nausea, nervousness

Less effective than HT but limited evidence

SSRI's: avoid tamoxifen
- Citalopram (Celexa)10-20 mg/day
- Escitalopram (Lexapro)10-20 mg/day

SNRI's: do not inhibit CYP2D6
- Venlafaxine (Effexor)37.5 to 75 mg/day :
- Desvenlafaxine (Pristeq) 100-150mg/day



Nelson h, et all. Nonhormonal therapies for menopausal hot flashes: systemic review and meta-analysis. JAMA 2006

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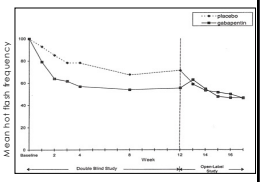
Other off label use of medications for hot flashes

- Gabapentin
  - -Side effects of lethargy and sedation
  - -As effective as SSRI but crossover study women preferred SSRI/SSNI with breast cancer
- Clonidine: a-2-andrenergic receptor agonist
  - -Side effects of hypotension, bradycardia, dizziness, headache, constipation, dry mouth
- Oxybutynin: antimuscarinic/anticholinergic for overactive bladder
  - -Use in patient with overactive bladder
  - -cognitive side effects in older women



JAMA Intern Med. 2019;179(8):1084-1093. doi:10.1001/jamainternmed.2019.0687 Published online June 24, 2019. Simon JA et al. Menopause.2016;23(11):1214-1221. Leon-Ferre et al. Presented SABC December 2018 Bordeleau et. Al. Multicenter, randomized, crossover clinical trail of venlafaxine vs gabapentin for breast cancer survivors. J Clin Oncol 2010

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Veozah: Fezolinetant 45mg

VEOZAH (fezolinetant) tablets 45mg

- Selective Neurokinin 3 Receptor antagonist to block NKB (trigger for VMS)
- Contraindicated in cirrhosis, renal impairment
- Liver Function tests:
  - ALT,AST, bilirubin, Alk phos
  - -1,2,3,6,9,12 MONTHS
- Side effects: abdominal pain, diarrhea, jaundice, insomnia, back pain, vomiting, jaundice
- Contraindicated with CYP1A2 inhibitors

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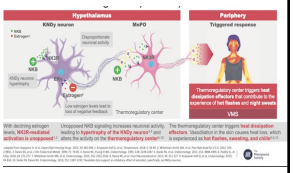

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CYPA12 inhibitors contraindicated with Veozah

- Warfin
- Citalopram
- Paroxetine
- Ketoconazole
- Clarithromycin
- Ciprofloxacin
- Erythromycin
- cimetidine
- Verapamil
- diltiazem

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Sexual Dysfunction

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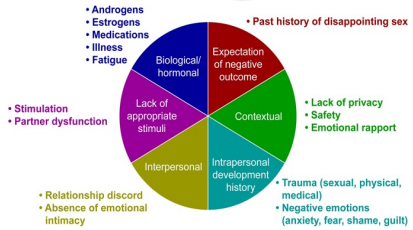
Components of midlife women's sexual interest/function



Basson R *J Sex Marital Ther* 2001;27:33-43; Dennerstein L *Climacteric* 1999;2:254-62

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Female sexual dysfunction

1. **Sexual desire, interest**
2. **Sexual pain (Genito-pelvic pain/penetrations disorder)**
3. Female Orgasmic disorders
4. Arousal Disorder
5. Other specified sexual dysfunction and other unspecified sexual dysfunction

- Counseling
- Couples therapy
- Psychotherapy
- Lifestyle changes
- Treating pelvic floor therapy
- Vaginal estrogens
- Medications

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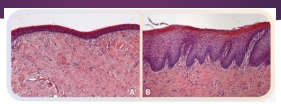
Genitourinary syndrome of menopause



- Loss vaginal rugae and elasticity
- Epithelial loss tissue more fragile →bleeding, brown or yellow discharge
- Loss of subcutaneous fat in labia majora
- Vaginal ph more alkaline →urogenital infections
- Dyspareunia

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Non-hormonal treatment for Gentourinary syndrome of menopause

Moisturizers

- Does not cure atrophy
- Allows cells to retain moisture
- Use vaginally every four days
- Attaches to vaginal epithelium
- Reduces pain, itching, irritation
- *Replens®, Me Again™, Feminine Moisturizer, Femenease®, and K-Y® SILK-E®.*
- Revaree (hyaluronic acid)

Lubricants

- Reduce friction during sex
- WHO: lubricants with <380 mOsm/kg
- may be associated with vaginal irritation
- Parabens, glycerin, warming, flavors, and spermicides should be avoided because they may irritate vaginal and vulvar tissues.
- natural oils (e.g., olive, coconut) can be associated with vaginal infections

Nonpharmacological

- **Vaginal dilators**
  improving vaginal elasticity
- **Vibratory stimulation**
  applied to vagina or clitoris
- **Vaginal C02 Laser**
  Not fda approved, limited data
  Not shown superior ET, safety risks

NAMS, 2012; Feldhaus-Dahir, 2010, Jokar et al., 2016; Chen, 2013
NAMS 2020 Postion statement GSM of NAMS, menopause vol27,no9 pp 976-992

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Vaginal Estrogen

- **Systemic Estrogen may not effective**
- **Low dose vaginal estrogens do not increase estradiol blood levels in RCT**
  - -No progesterone needed **(except the femring)**
  - -Can be used with caution in patients with contraindications to systemic estrogen
  - -little to no effect on prothrombotic factors in RCT and observational studies
  - -breast cancer patients
- **despite the same labeling, it does not have the same risk as systemic estrogen**

Faubion et al. 2020 GSM position statement of NAMS. Menopause vol 27, no 9, 2020
Faubion et al. Management of GSM in women at high risk for breast cancer. Menopause vol 25, No 6 2018

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Hormonal tx: Local Estrogen Vaginal Preparations

Cream:
- Premarin: 0.625 mg CEE/g cream with dosage 0.5-1 g twice a week
- Estrace: 100 mcg estradiol/ g cream with 1-2 g twice a week

Vaginal Inserts:
- Imvexxy: 4ug and 10ug estradiol
- Vagifem/yuvafem : 10mg estradiol tablet twice a week

RING:
- Estring: 7.5 mcg estradiol
- Femring: 12.4 and 24.8 estradiol acetate (NEED PROGESTERONE FOR ENDOMETRIAL PROTECTION)

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Non-estrogen options for dyspareunia

Ospemiphine (SERM) oral 60mg daily
- Oral medication: good for limited mobility or pain (arthritis, vulvodynia)
- Agonist on the vaginal tissue, potential for uterine tissue
- Studies of breast cancer show similar effect to other antiestrogens such as tamoxifen & raloxifene on breast tissue: off label in US
- Side effects: 25% hot flashes, risk of thromboembolism , muscle spasms, rash

Intravaginal DHEA: Intrarosa
- Vaginal Prasterone 6.5mg once a day
- Limited studies with breast cancer population – Estrogen is a *metabolite* of DHEA
- Use with caution in women with androgen-receptor positive breast cancer

Wurz G, Et al. Ospemifen, vulvovaginal atrophy &BC. Maturitas 2013;74:220-225
Barton D, et al evaluating af of vaginal DHEA in PM BC survivors. Support Care 2018;26:643-50

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ACOG The American College of Obstetricians and Gynecologists

CLINICAL CONSENSUS

NUMBER 2
DECEMBER 2021
(REPLACES COMMITTEE OPINION NO. 650, MARCH 2016)

Treatment of Urogenital Symptoms in Individuals With a History of Estrogen-dependent Breast Cancer

Committee on Clinical Consensus–Gynecology. This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Clinical Consensus – Gynecology in collaboration with committee member Betty Suh-Burgmann, MD, and liaison Elizabeth Evans, MD

- Non hormonal therapies remain first line
- Next low dose vaginal estrogen with shared decision making
- Studies showed several vaginal estrogen formulations keep E Serum levels <20 pg/ml
- With Aromatase inhibitors , potential for elevated serum estrogen levels
  - however in 10 studies, none noted
- No increase recurrence as well changes in Bi-RADS scores
- Ospemifene (SERM) may be considered an option for estrogen dependent breast cancers
  - FDA warning to not use but used in Europe

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Not working??

1. Using the medication correctly and often enough?
2. Is there a Vulva Dermatosis?
3. Is there an infection ?
4. Is there pelvic floor dysfunction or Vaginismus?
5. Is there another etiology such as vulvodynia , vestibulodynia?

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Hypoactive sexual desire disorder

- Persistent or recurrent deficiency or absence for sexual thoughts, fantasies, and/or desires for sexual activity
  - -**causes marked personal distress** or interpersonal difficulties
  - -Not caused by medication or medical condition
- Through clinical evaluation with identification, modification and management of biological , phycological, sociocultural, and interpersonal factors before tx
- Evaluation of arousal, orgasm, pain with targeted gynecologic exam
- **12% of women in US**
- Screening Questionnaire

Decreased Sexual Desire Screener (DSDS)

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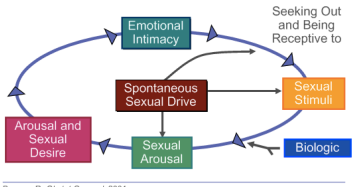
Sexual Response Model

Female Sexual Response - Circular



Basson, R. *Obstet Gynecol*. 2001.

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Hypoactive sexual desire disorder treatment

Psychotherapy

- Psychoeducation
- couples exercises
- sensate focus
- individual and group psychotherapy: AASECT

Pharmacologic treatment

- Addyi
- Vylessi
- Testosterone (off label postmenopausal women)

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Addyi (Flilbasertin)

Addyi (Flibasertin)

- FDA approved in 2015 as an oral non-hormonal pill for HSDD in PREMENOPAUSAL WOMEN
- Serotonin receptor agonist/antagonist that results in transient decreases in serotonin and increased in dopamine and norepinephrine
- Women advised to only drinks1-2 drinks alcohol and stop at least 2 hrs before taking at bedtime or skip
  - Box warning label with alcohol removed
- Adverse side effects SYNCOPE, HYPOTENSTION, sleepiness, nausea fatigue, insomnia and dry mouth
- Contraindicated in patients with hepatic impairment or medications with CYP3A4 inhibitors (fluconazole)
- Increased 0.4 to 1.0 addition "SATISFYING SEXUAL EVENTS" month
- No data to support improvement for women on SSRI

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Bremelanotide (Vylessi)

- Melanocortin receptor agonist to increase dopamine, serotonin, Norepinephrine
- FDA approved June 2019 for premenopausal women
- Subcutaneous injection 45 minutes before anticipated sexual activity
- No difference in satisfying sexual events but increase in sexual desire 51 vs 21 % and improvement in sexual satisfaction 57 vs 26%.
- Side effects include nausea 40%, vomiting 5%, flushing 20%, headache 11%, hyperpigmentation 1%, transient increase in blood pressure

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Testosterone

Global Consensus Position Statement on the use of Testosterone Therapy for Women*

Susan R. Davis[a,b,*], Rodney Baber[b,c], Nicholas Panay[d,e], Johannes Bitzer[f,g], Sonia Cerdas Perez[h,i],

- The only evidence-based indication for testosterone therapy for women is HSSD in **postmenopausal** women
- Meta-analysis shows no adverse effects in low risk women (high CVD risk excluded)
- Long term safety has NOT been established.
- Blood levels should not be used to diagnose HSDD, Testosterone formations should target normal physiological levels **within** premenopausal levels
- Compounded testosterone preparations are not recommended
- Male formulations can be judiciously used in female doses with serum testosterone concentrations monitored regularly
- More research is needed for women.

Journal of sexual medicine 2019Sept 16(9):1331-1337
Climacteric, 22:5,429-434
J of clin Endo, 104(10):1-7
Maturitas 2019 Jul:7

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Testosterone Therapy

THE JOURNAL OF SEXUAL MEDICINE

International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women

- 1/10 standard male dose of 1% transdermal testosterone (5mg/0.5mL) or about 300mcg/day
  - pea sized amount to back of calf or thigh to avoid transference (1 tube/10 days)
- Testing with **total testosterone** levels and SHBG levels to keep physiological range
  -3 to 6 weeks after initiation or increase dose , 2-3 weeks if supraphysiologic
  -repeat 4-6 months to screen for overuse
- Efficacy usually within 6-8 weeks. Max by 12 weeks . No benefit in 6 months then stop
- Consider trial drug holiday after 12 months
- Annual breast/pelvic, mammo, lipids, LFTs, cbc (labs Q6-12mths), r/o androgen excess
- Side effects: acne & Hair growth.
- Potential for voice deepening, alopecia, breast cancer , CHD

ISSWSH

Sharon Jet al J Sex Med 2021 May;18(5):869-867.

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Summary

1. Contraception not only prevents pregnancy but can help with perimenopausal symptoms. . Progesterone only contraception can be used in conjunction with ET to treat VMS in some women who have contraindication to COC.
2. A variety or hormonal and nonhormonal options exist to treat VMS. Hormone therapy is most the effective tx with high benefit to risk ratio in women < 60yrs and 10 yr from LMP. Risks differ for women depending on doses, duration, formulation and timing of initiation .
3. Hormonal and nonhormonal tx are effective treatments for genitourinary syndrome of menopause . Although product label for low dose vaginal ET note risks associated with systematic HT, clinical trials show that these risks are highly unlikely due to minimal systemic absorption.
4. Sexual dysfunction among women is common and is usually multifactorial. Pharmacological treatment can help with along with a biophysical approach for improving sexual health. While there are no FDA approved medications for postmenopausal women, 1/10 of dose male formulations can be used safely with monitoring.

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NYT: Puberty for the Middle-Aged

By Lisa Selin Davis.
Nov. 19, 2018

Forty-five-year-old women need a version of "the talk," because our bodies are changing in ways that are both really weird and really uncomfortable.

"If only, on your 45th birthday, a doctor would sit you down, look you squarely in the eyes and say, Here's what's going to happen..."

"We put a lot of time and effort into preparing teenagers for what changes puberty will wreak, but for women, midlife brings another kind of puberty—perimenopause..."

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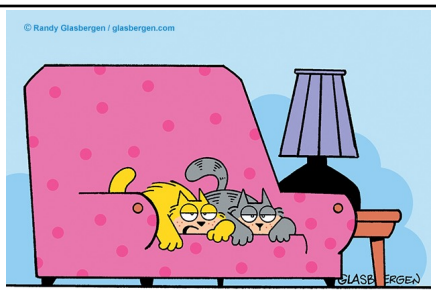

"Having nine lives is cool, but if I have to go through menopause again, forget it!"

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