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18TH ANNUAL WOMEN'S HEALTH UPDATE 2022

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PRACTICAL TIPS FOR PRESCRIBING HORMONE THERAPY

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DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INDUSTRY

- None

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Nothing to disclose

LEARNING OBJECTIVES

- Review the nuances of clinical decision-making in prescribing menopausal hormone therapy
- Discuss the use of menopausal hormone therapy in women with chronic medical conditions
  - Obesity
  - Hypertension
  - Hyperlipidemia
  - Diabetes
  - Venous thromboembolism
  - Autoimmune disease

INDICATIONS FOR USE OF MHT

- Vasomotor and other menopause symptoms (mood, sleep) management
  - First line therapy for relief of menopause symptoms in appropriate candidates
- Prevention of bone loss
  - RCT evidence for reduction of bone loss
  - Reduced fracture risk in postmenopausal women-WHI
- Treatment of premature hypoestrogenism
  - Premature ovarian insufficiency
    - Bilateral salpingo-oophorectomy before natural menopause
- Genitourinary symptoms
  - RCT evidence for restoration of genitourinary anatomy, reduction in pH and symptoms of GSM, increase in superficial vaginal cells

NAMS 2017 position statement; Menopause 2017; 24(7)

WHO IS THE BEST CANDIDATE FOR MHT?

- Women <age 60, <10 years past menopause
- Bothersome symptoms (VMS, mood, sleep)
- Bone density concerns (2nd line therapy)
- Personal preference to use MHT
- **No excess CV or breast cancer risk**
- No contraindications

NAMS 2017 position statement; Menopause 2017; 24(7)

CONTRAINDICATIONS TO MHT USE

- Unexplained vaginal bleeding
- Prior estrogen sensitive cancers (breast/endometrium)
- History of stroke, MI, or dementia
- History of or inherited high risk for VTE
- Severe active liver disease

Caution:

- Endometriosis may reactivate
- Migraine may worsen
- Leiomyomas may grow

NAMS 2017 position statement; Menopause 2017; 24(7)

VASOMOTOR SYMPTOMS

- Prevalent-75% of women
- Duration
  - 7-10 years
  - Longer in women whose symptoms begin in perimenopause (>11 years)
  - Worse in women with obesity
  - 6.5% of women aged 60-65 years in a community-based sample still reported moderate-severe vasomotor symptoms

Image from clip art

Freeman EW et al. Menopause 2014. 21:924–32. Avis N.E., et al. JAMA internal medicine, 2015. 175(4): p. 531-9. Gartoulla P. Menopause 2015. 22(7): 694-701.

VASOMOTOR SYMPTOMS

Associations

- Poorer quality of life
- Sleep problems
- Negative mood
- Lower bone density
- Subclinical cardiovascular disease

Risk Factors

- Low education
- Smoking
- Negative affect
- Obesity
- Adverse childhood experiences

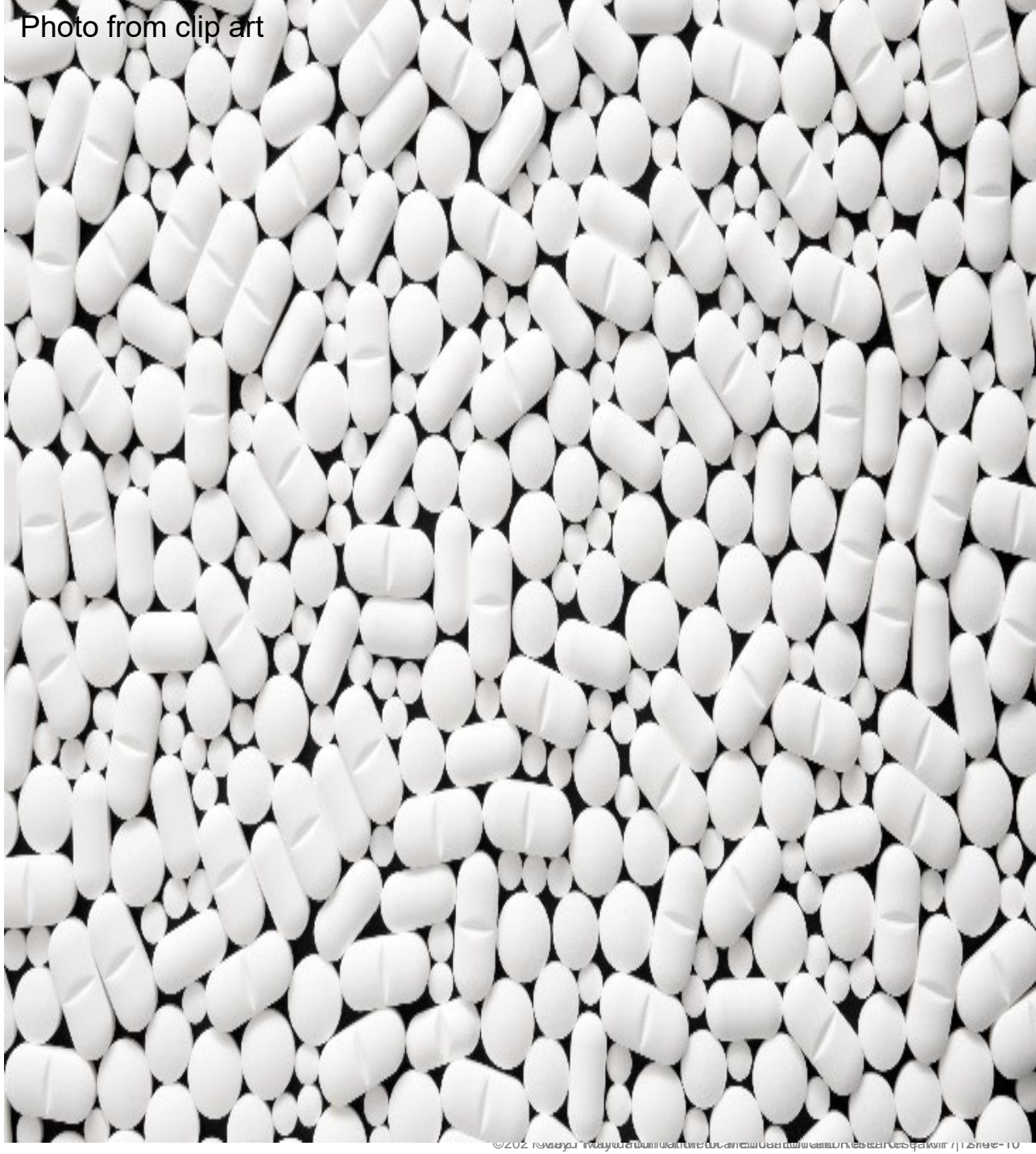
Thurston RC, Joffe H. Vasomotor Symptoms and Menopause: Findings from the Study of Women's Health Across the Nation. Obstet Gynecol Clin North Am. 2011; 38(3): 489-501. Thurston RC et al. Childhood abuse or neglect is associated with increased vasomotor symptom reporting among midlife women. Menopause 2008; 15(1): 16-22.

ROUTE OF ESTROGEN ADMINISTRATION

TRANSDERMAL MAY HAVE SAFETY ADVANTAGES OVER ORAL

- Less effect on:
  - Clotting factors
  - Blood pressure
  - Triglycerides
  - C-reactive protein
  - SHBG

Lokkegaard et. al. Eur Heart J. 2008; Modena Maturitas, 2005; Vongpatanasin. J Am Coll cardiol 2003; Hemelaar Fertil Steril 2008; Stuenkel CA, et al. J Clin Endocrinol Metab 2015; 100:3975-4011.



ORAL ESTROGENS AVAILABLE IN THE US

Estrogen type	Name of product	Common Dosages, mg/d
Conjugated estrogen	Premarin	0.3, 0.45. 0.625, 0.9, 1.25
Synthetic conjugated estrogen	Cenestin	0.3, 0.45, 0.625, 0.9, 1.25
Esterified estrogen	Menest	0.3, 0.625, 1.25, 2.5
17β estradiol	Estrace, various generics	0.5, 1.0, 2.0

TRANSDERMAL ESTROGENS AVAILABLE IN THE US

Estrogen type	Name of product	Common Dosages, mg
17β estradiol matrix patch	Alora, Climara, Vivelle, Vivelle-Dot, Minivelle, multiple generics	0.025 to 0.1 once or twice/week, depending upon the patch
17β estradiol reservoir patch	Estraderm	0.05, 0.1 twice/week
17β estradiol transdermal gel	EstroGel Divigel	0.035/d 0.25, 0.5, and 1.0 g/d
17β estradiol transdermal spray	Evamist	0.021/90μL/d (increase to 1.5/90μL/d if needed)
17β estradiol topical emulsion 17β estradiol topical emulsion (estradiol hemihydrate 2.5mg/g)	Estrasorb	0.05/d (2 packets)

EQUIVALENT ESTROGEN DOSES IN MHT

- Oral conjugated estrogen: 0.625 mg
- Oral esterified estrogen: 0.625 mg
- Oral 17β-estradiol: 1 mg
- Transdermal estradiol patch: 0.05 mg
- Transdermal estradiol gel: 1.5 mg/2 metered doses (Divigel 0.1 mg/d)

PROGESTOGENS COMMONLY AVAILABLE IN THE US

Progestogen type	Name of product	Dosages/d
Oral progesterone: micronized progesterone in peanut oil	Prometrium or generic equivalent	100 mg or 200 mg (given daily or cyclically)
Oral progestins 1. Medroxyprogesterone acetate 2. Norethindrone* 3. Norethindrone acetate*	 Provera or generic equivalent Micronor or generic equivalent Aygestin or generic equivalent	 2.5 mg, 5 mg, 10 mg 0.35 mg 2.5 mg
Intrauterine levonorgestrel* (**contraception, manage abnormal uterine bleeding**)	Mirena Skyla Kyleena	20 µg/d 6 µg/d 7.5 µg/d

***Not FDA-approved for hormone therapy**

Combination estrogen-progestogen hormone therapy products

Product type	Name of product	Dosages, mg/d
Oral continuous regimens		
1. 17β estradiol + progesterone	Bijuva	1 mg + 100 mg
2. Conjugated estrogen + MPA	Prempro	0.625 mg + 2.5 or 5 mg 0.3 or 0.45 mg + 1.5 mg
3. Ethinyl estradiol + NETA	Femhrt	2.5 µg + 0.5 mg or 5 µg + 1 mg
4. 17β estradiol + NETA	Activella	0.5 mg + 0.1 mg or 1 mg + 0.5 mg
5. 17β-estradiol + drospirenone	Angeliq	0.5 mg + 0.25 mg
Oral continuous cyclic regimen Conjugated estrogen (E) + MPA (P)	Premphase	0.625 mg + 5.0 mg (E alone for days 1-14, followed by E + P on days 15-28)
Oral intermittent regimen 17β-estradiol (E) + norgestimate (P)	Prefest	1 mg + 0.09 mg (E alone for 3 d, followed by E+P for 3 d, repeated continuously
Transdermal continuous regimens		
1. 17β-estradiol (E) + NETA (P)	CombiPatch	0.05 mg E + 0.14 mg P patch, twice/wk; 0.05 mg E + 0.25 mg P patch, twice/wk)
2. 17β-estradiol + LNG	ClimaraPro	0.045 mg + 0.015 mg patch, once/wk)

MPA: medroxyprogesterone acetate
NETA, norethindrone acetate
LNG: levonorgestrel

FDA-APPROVED BIOIDENTICAL HORMONE PREPARATIONS

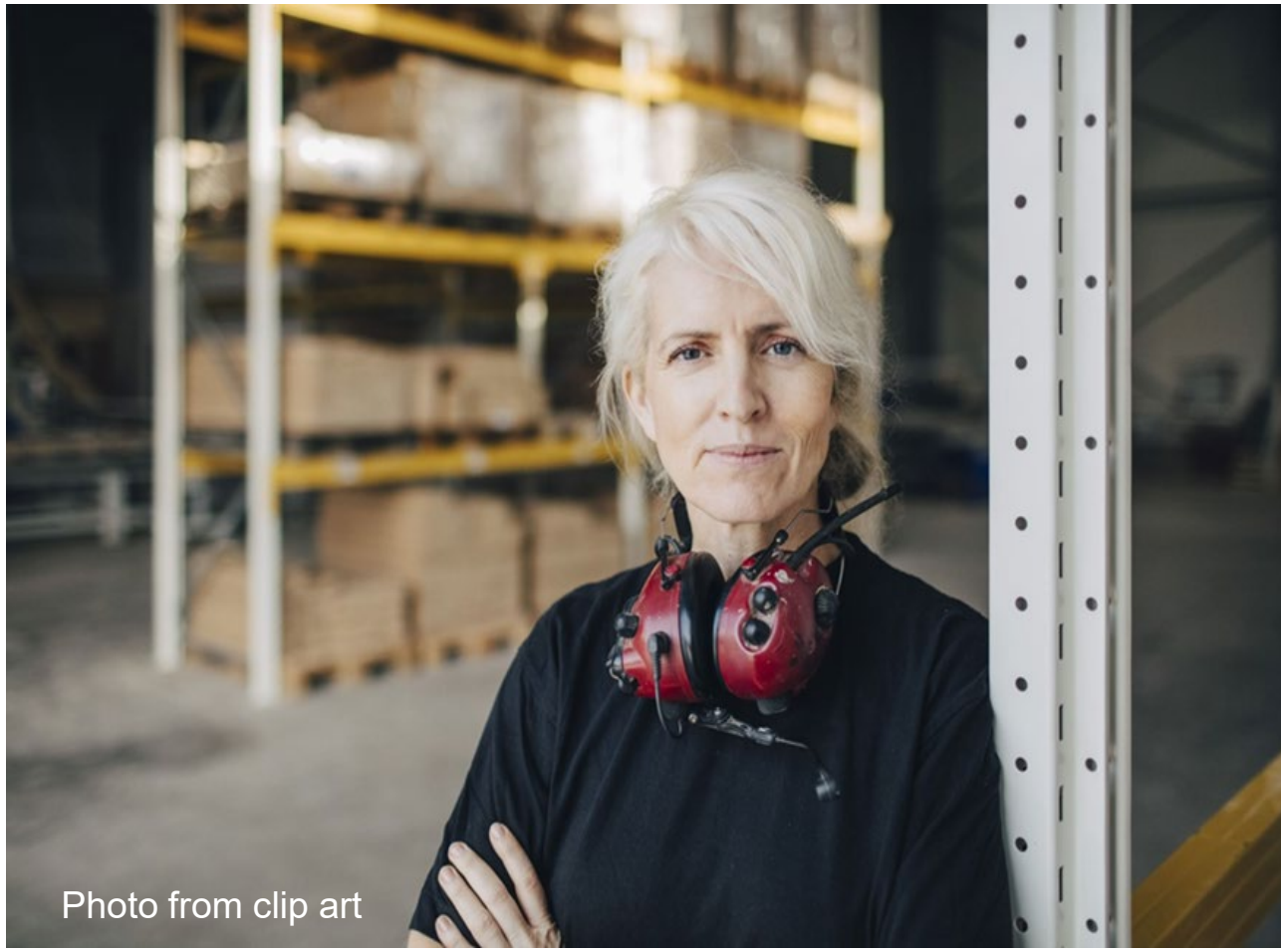
- Estrogen preparations
  - Oral 17-β estradiol
  - Cutaneous 17-β estradiol preparations:
    - Patches, gels, sprays, and emulsions
- Progesterone
  - Oral micronized progesterone
  - AVOID MEDROXYPROGESTERONE ACETATE

Stuenkel CA, et al. J Clin Endocrinol Metab 2015; 100:3975-4011.

Age at onset of menopause	With uterus	Without uterus
Age <40 to 45 years with or without symptoms **Continued until at least the age of natural menopause (age 50 to 51 years)**	Estradiol patch (0.1 mg/24 hours) or oral estradiol (2 mg daily) and cyclic progesterone (200 mg nightly for 12 days in a row each month)	Estradiol patch (0.1 mg/24 hours) or oral estradiol (2 mg daily)
Age late 40s to early 50s with symptoms **Reassessed yearly**	Estradiol patch (0.05 mg/24 hours) or oral estradiol (1 mg daily) and cyclic progesterone (200 mg nightly for 12 days in a row each month)	Estradiol patch (0.05 mg/24 hours) or oral estradiol (1 mg daily)
Age late 50s to 60s with symptoms **Reassessed yearly**	Estradiol patch (0.025 to 0.0375 mg/24 hours) or oral estradiol (0.5 to 1 mg daily) and cyclic progesterone (200 mg nightly for 12 days in a row each month) or continuous progesterone (100 mg nightly) **Note:** micronized progesterone is not ideal for patients with risk factors for endometrial malignancy	Estrogen patch (0.025 to 0.0375 mg/24 hours) or oral estradiol (0.5 to 1 mg daily)

WOMEN WITH HYPERTENSION

- HTN is the most common modifiable CVD risk with a global prevalence in women of 30%
- It is more common in men < 50 yrs, but trend reverses in midlife when it becomes more common in women



Kapoor E, Kling JM, Lobo AS, Faubion SS. Menopausal hormone therapy in women with medical conditions. Best Pract Res Clin Endocrinol Metab. 2021.

WOMEN WITH HYPERTENSION

- MHT often avoided in women with HTN due to belief it increases BP
- Current evidence does not support deleterious effect of MHT on BP in young postmenopausal normotensive or hypertensive women (may not be true for older postmenopausal women)
- Synthetic progestogens linked with BP increase
- Transdermal E has shown a beneficial effect on BP in normotensive women; neutral effect in hypertensive women
- Recommendation:
  - Consider overall CVD risk
  - Transdermal E preferred
  - Prefer micronized progesterone (beneficial or neutral BP effect)

Kapoor E, Kling JM, Lobo AS, Faubion SS. Menopausal hormone therapy in women with medical conditions. Best Pract Res Clin Endocrinol Metab. 2021

WOMEN WITH OBESITY

Photo from clip art

- Weight gain in midlife is predominantly related to aging rather than menopause
- Body composition changes are menopause-related
- Obesity confers increased risk for CHD, VTE, breast and endometrial cancers
- Obese women are more likely to have severe/frequent VMS

Kapoor E, Kling JM, Lobo AS, Faubion SS. Menopausal hormone therapy in women with medical conditions. Best Pract Res Clin Endocrinol Metab. 2021

WOMEN WITH OBESITY

- MHT has not been consistently shown to impact weight, but it has a favorable effect on body composition and fat distribution
  - Preserves lean body mass
  - Reduces visceral adiposity
- Observational data shows lower risk of CVD and related mortality with transdermal E
- Recommendation:
  - Use transdermal over oral E preparations
  - Consider progestogen with lower risk of VTE and minimal effects on metabolic parameters: micronized progesterone

Kapoor E, Kling JM, Lobo AS, Faubion SS. Menopausal hormone therapy in women with medical conditions. Best Pract Res Clin Endocrinol Metab. 2021.

WOMEN WITH DYSLIPIDEMIA

- Menopause transition is linked with
  - Increases in LDL-C and apolipoprotein B
  - Functional changes in HDL-C as well as altered HDL particle distribution resulting in a reversal in the direction of association between HDL-C and CVD risk
- In combination with adverse changes in BP and glucose ⇨ increased metS

Photo from clip art

Kapoor E, Kling JM, Lobo AS, Faubion SS. Menopausal hormone therapy in women with medical conditions. Best Pract Res Clin Endocrinol Metab. 2021.

WOMEN WITH DYSLIPIDEMIA

- In women with dyslipidemia, consider overall CVD risk
  - Avoid MHT in women with pre-existing CVD and those at high risk for CVD
- MHT has favorable or neutral effects on lipid parameters and overall CVD risk
  - Oral E decreases LDL-C and lipoprotein(a) levels and increases HDL-C and triglycerides
  - Transdermal E may lower total and LDL-C with neutral effect HDL-C and triglycerides
  - MHT effects on lipoproteins are dose dependent
- Recommendation:
  - Use transdermal over oral E in women with pre-existing hypertriglyceridemia, moderate risk of CVD and in women with comorbidities such as obesity, HTN, DM

Kapoor E, Kling JM, Lobo AS, Faubion SS. Menopausal hormone therapy in women with medical conditions. Best Pract Res Clin Endocrinol Metab. 2021.

WOMEN WITH DIABETES


Photo from clip art

- Substantial evidence that MHT improves glycemic control and insulin resistance in postmenopausal women with and without T2DM
  - Meta-analysis 107 trials: MHT reduced HOMA-IR by 13%; reduced risk of T2DM by 30%
  - In women with T2DM, HOMA-IR reduced by 36% in addition to improvements in other CVD risk factors, including lipids, BP and coagulation markers

Kapoor E, Kling JM, Lobo AS, Faubion SS. Menopausal hormone therapy in women with medical conditions. Best Pract Res Clin Endocrinol Metab. 2021.

WOMEN WITH DIABETES

- Greater benefit of oral E versus transdermal
- Use of MHT in women with T2DM is about 50% lower than general population
- Don’t avoid MHT, but individualize
  - Oral only in normal weight women at low risk of CVD
  - Transdermal in women with obesity or moderate risk of CVD
    - More favorable effects on inflammatory markers and triglycerides
    - Lower risk of VTE
  - Micronized progesterone appears to have minimal effects on glycemic control

Kapoor E, Kling JM, Lobo AS, Faubion SS. Menopausal hormone therapy in women with medical conditions. Best Pract Res Clin Endocrinol Metab. 2021.

WOMEN WITH VENOUS THROMBOEMBOLISM

- Overall incidence of VTE increases with age, nearly doubling for women from age 25 to 50 years (51 to 123 per 100,000 per year)
- Female specific risks include pregnancy and use of OCPs
- Other risks: obesity, major surgery, trauma, immobility, malignancy, previous VTE, smoking


Photo from clip art

Kapoor E, Kling JM, Lobo AS, Faubion SS. Menopausal hormone therapy in women with medical conditions. Best Pract Res Clin Endocrinol Metab. 2021.

WOMEN WITH VENOUS THROMBOEMBOLISM

- Risk of VTE with MHT is elevated versus placebo, but risk is lower if started in women within 10 years of menopause
- Dose and route of administration matter
  - Lower doses and transdermal formulations of systemic E associated with lower risk in observational studies
    - One study of women with VTE showed that oral but not transdermal E was associated with higher risk of recurrent VTE
  - RCT safety data (52 weeks) and longer-term observational data do not indicate increased risk with low dose vaginal E therapies (package insert does not distinguish between systemic and low dose vaginal E)

Kapoor E, Kling JM, Lobo AS, Faubion SS. Menopausal hormone therapy in women with medical conditions. Best Pract Res Clin Endocrinol Metab. 2021

WOMEN WITH VENOUS THROMBOEMBOLISM

- Progestogen influences risk
  - Lower risk with micronized progesterone
- Recommendation:
  - Use shared decision making taking into account individual risk factors such as thrombophilia, severity of symptoms and impact on QOL
  - Review non-hormonal options
  - Transdermal route if E is used

Kapoor E, Kling JM, Lobo AS, Faubion SS. Menopausal hormone therapy in women with medical conditions. Best Pract Res Clin Endocrinol Metab. 2021.

WOMEN WITH AUTOIMMUNE DISEASE


Image from clip art

- Autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjogren's syndrome (SS) and multiple sclerosis (MS) are more common in women, with a second peak in incidence in midlife
- Hypothesis that there is a link between menopause and autoimmune disease risk and course
- Changing estrogen levels may be a modifying factor
  - Earlier age at menopause linked with increase risk of SLE, RA and progressive MS
  - Symptoms of SS may worsen

Kapoor E, Kling JM, Lobo AS, Faubion SS. Menopausal hormone therapy in women with medical conditions. Best Pract Res Clin Endocrinol Metab. 2021

WOMEN WITH AUTOIMMUNE DISEASE

- Unknown if MHT may mitigate or reduce autoimmune disease incidence, risk or severity
  - Some reports of lower risk of autoimmune disease in general and fewer symptoms in those with RA with some forms of MHT
  - No reports of severe SLE exacerbations with MHT initiation
  - Estradiol has been explored as a treatment for MS
    - Beyond relief of menopausal sx, MHT has been shown to improve physical function in women with MS
- Recommendation:
  - MHT can be considered if no other contraindications to use
  - Avoid in women with antiphospholipid syndrome
  - Data sparse in women with SS, but consider the addition of low dose vaginal hormonal therapy to treat genitourinary symptoms

Kapoor E, Kling JM, Lobo AS, Faubion SS. Menopausal hormone therapy in women with medical conditions. Best Pract Res Clin Endocrinol Metab. 2021.

MONITORING PATIENTS ON HORMONE THERAPY

- Symptom control
- Assess for adverse effects and development of contraindications
- Annual breast cancer screening
- No need to check estradiol level unless concerned about malabsorption
  - Check serum estradiol (not salivary hormone levels)
  - No goal estradiol level-treat the symptoms

WHEN TO CONSIDER STOPPING MHT?

- Lack of RCT data to inform decision making
- Expert opinion
  - Review of risks/benefits
  - Reasonable to attempt dose reduction around age 60
    - Symptom trajectory favorable
    - Breast cancer risk increases with years of use

Faubion SS, Kaunitz AM. Stopping systemic menopausal hormone therapy: Why, when and how. Maturitas 2016; 89:3-4.
Kaunitz AM. Extended duration use of menopausal hormone therapy. Menopause 2014;21(6):679-81.

CONSIDERATIONS FOR LONG-TERM USE

- Reasons to consider
  - Persistent vasomotor symptoms
  - Quality of life concerns/patient preference
  - Prevention of osteoporosis in women at increased risk for fracture

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

CONSIDERATIONS FOR LONG-TERM USE

- If patient chooses to remain on MHT
  - Lowest dose needed to control symptoms/meet treatment goals
- Assess risks and benefits annually
- Breast cancer screening
- Individualize treatment and counseling

Practice Bulletin No.141. American College of Obstetricians Gynecologists. Obstet Gynecol 2014;123:202–16. The North American Menopause Society statement on continuing use of systemic hormone therapy after age 65. Menopause, 2015. 22(7):693. Faubion SS, Maturitas 2016; 89:3-4. Kaunitz AM. Menopause 2014;21(6):679-81.

HOW TO DISCONTINUE MHT?

- No “right” way to discontinue
  - Slow taper vs abrupt discontinuation
  - Reassure patient that last effective dose can be restarted if symptoms recur without follow up visit
- Monitor
  - VMS
  - Vaginal dryness
  - BMD

Practice Bulletin No.141. American College of Obstetricians Gynecologists. Obstet Gynecol 2014;123:202–16. The North American Menopause Society statement on continuing use of systemic hormone therapy after age 65. Menopause, 2015. 22(7):693. Faubion SS, Maturitas 2016; 89:3-4. Kaunitz AM. Menopause 2014;21(6):679-81.

CURRENT RECOMMENDATIONS

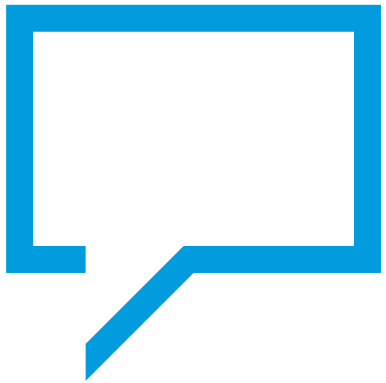
- Old: lowest dose for shortest period of time
- Now: appropriate MHT type, dose, formulation, route of administration and duration to meet treatment objectives
- HT should be individualized and reevaluated periodically to maximize the benefits as well as minimize the risks of use
- Not discontinued solely based on a woman's age

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

CONCLUSIONS

- There is a significant burden associated with untreated VMS
- Menopausal hormone therapy is first line therapy (and the most effective therapy) for vasomotor symptoms
- Women with certain chronic conditions may still be candidates for MHT

QUESTIONS & DISCUSSION



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