Managing Menopause in Patients with Chronic Medical Conditions

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1

Disclosure

I have no financial interests or relationships to disclose.

2

Learning Objective

After this lecture, you will be able to:

- Individualize hormone therapy for symptomatic menopausal people with HTN, HLD, obesity, T2DM, autoimmune disorders, VTE, BRCA, and POI

3

Individualizing

- Risks/benefits differ for different people depending on
  - Dose
  - Route of administration
  - Timing of initiation
  - Progestin or not?
- Periodic reevaluation

4

US Preventative Services Task Force

Final Recommendation Statement

Hormone Therapy in Postmenopausal Women: Primary Prevention of Chronic Conditions

Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Postmenopausal women	The USPSTF recommends against the use of combined estrogen and progestin for the primary prevention of chronic conditions in postmenopausal women.	D
Postmenopausal women who have had a hysterectomy	The USPSTF recommends against the use of estrogen alone for the primary prevention of chronic conditions in postmenopausal women who have had a hysterectomy.	D

Grade D = evidence of no net benefit OR harms outweigh benefits

Mangione CM, Barry MJ, et al. Hormone Therapy for Primary Prevention of Chronic Conditions in Postmenopausal Persons: US Preventative Services Task Force Recommendation Statement. US Preventive Services Task Force, JAMA. 2022;328(17):1740-1746. doi:10.1001/jama.2022.18625.

5

Which of the Following Is an FDA-approved Indication for Use of HT?

A. Treatment of depression in menopause
B. Treatment of sleep disturbance in menopause
C. Treatment of persons at high risk for osteoporosis
D. Treatment of persons at high risk for dementia

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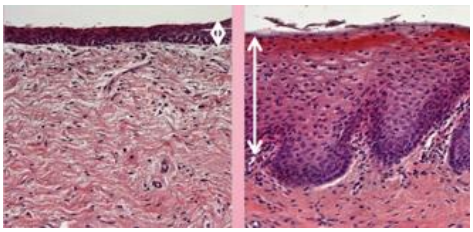
6

FDA-approved Indications for HT

- Treatment of vasomotor symptoms
- Treatment of GSM
- Use in medically or surgically menopausal women
- Prevention of osteoporosis in high-risk women



7

Which of the Following Is a Contraindication to Use of HT?

A. Patient is BRCA 2 gene positive
B. Patient has Type 2 diabetes on metformin
C. Patient's mother had breast cancer at age 62
D. Patient has acute active hepatitis

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8

Contraindications to HT

- Estrogen-dependent ca (mostly breast, some endometrial)
- Hx of VTE
- MI/Stroke/TIA/active CHD
- Active liver/gallbladder disease
- Unexplained vaginal bleeding or pregnancy

Not the same as OCPs (migraines, smoking not contraindications)
Family history not a contraindication
Always a risk-benefit discussion w/ individualized therapy

9

US
We Want to Choose the Most Effective and Safest Option for Our Patients.

80% of Women ≥ 55-years-old Have at Least 1 Chronic Medical Condition
1 in 5 Have Three or More Chronic Conditions

PATIENT
She Wants to Feel Better.

10

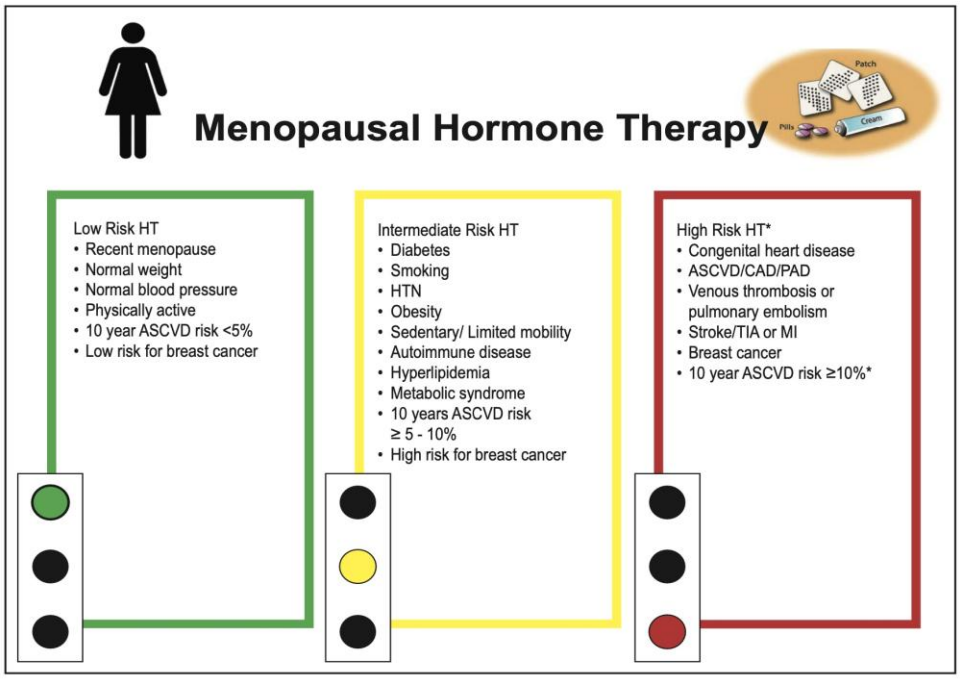
It's Not Just Symptoms; It's Long-term Health Too!

11

Common Comorbidities in Midlife

- HTN
- Dyslipidemia
- Obesity
- T2DM
- Autoimmune conditions
- VTE risk

12



Cho, L
Circulation
2023

13

O'Kelly Circ Research 2022

Contemporary Approach to HT

1. Evaluate age, time since menopause, and symptoms

<10 year from final menstrual cycle, <60 years old, and bothersome vasomotor symptoms

2. Perform ASCVD risk assessment and exclude HT contraindications

ASCVD risk factors

- Hyperlipidemia
- Hypertension
- Diabetes
- Family history of premature CVD in first-degree relative (men <55 or women <65 years of age)
- Obesity (BMI >30 kg/m^2)
- Physical inactivity
- Cigarette smoking
- Coronary calcification (moderate risk: CAC 1-99; high risk: CAC >100)
- History of preeclampsia
- History of systemic autoimmune collagen-vascular disease (e.g., lupus, rheumatoid arthritis)

Contraindications to systemic HT:

Coronary heart disease, stroke, TIA
Breast or endometrial cancer
History of pulmonary embolus, venous thrombosis or clotting disorder
Active liver disease
Undiagnosed abnormal vaginal bleeding

3. Evaluate risk category

May consider HT	***May consider HT, transdermal formulation***	***Not recommended to use HT:***
ASCVD risk <5% (low risk) and ≤1 CVD risk factor	ASCVD risk 5-10% or ASCVD risk <5% but ≥2 CVD risk factors	Age ≥60 or >10 years since menopause onset or ASCVD risk >10%

4. Ensure routine follow-up with re-evaluation of risks and benefits

14

Gaby: 49-year-old Teacher

She was told she cannot take HT because It will increase her blood pressure

- Hot flashes, night sweats, sleep issues, brain fog, and irritability
- HTN, well controlled on single drug therapy
- Fam hx of heart disease
- LMP 1 yr ago
- Vitals, labs, exam unremarkable

15

What Do You Offer Gaby?

A. Tell her to get a fan and tough it out.
B. Prescribe paroxetine 7.5 mg nightly.
C. Start TD estradiol 0.05 mg biweekly and micronized progesterone 100 mg nightly.

Women with Hypertension

- HTN is the most common modifiable CVD risk with a global prevalence in women of 30%
- More common in men < 50 yo, but trend reverses in midlife when it becomes more common in women
- HT often avoided in women w HTN due to belief it increases BP

17

Hypertension and HT

- TD estradiol and micronized progesterone have neutral effects on BP
- Oral estradiol and synthetic progestins (MPA) linked w BP increase
  - Oral E increases renin substrate
- TD estradiol has beneficial effects on BP in normotensive women, neutral effects on hypertensive women

18

Recommendation

- HTN should be well controlled
- Consider overall CVD risk
- Discuss BP-lowering diet
- TD estradiol and micronized progesterone preferred

19

Disease-Specific Recommendations

- **Hypertension**
  Reduce sodium, alcohol, and caffeine
  Increase
  - Potassium—potatoes, sweet potatoes, cantaloupe, bananas, peaches, squash, broccoli, spinach
  - Calcium—greens, beans, fortified non-dairy milk or low-fat dairy
  - Magnesium—almonds, cashews, peanuts, beans, quinoa, avocados, potatoes
  - Garlic
  - Water

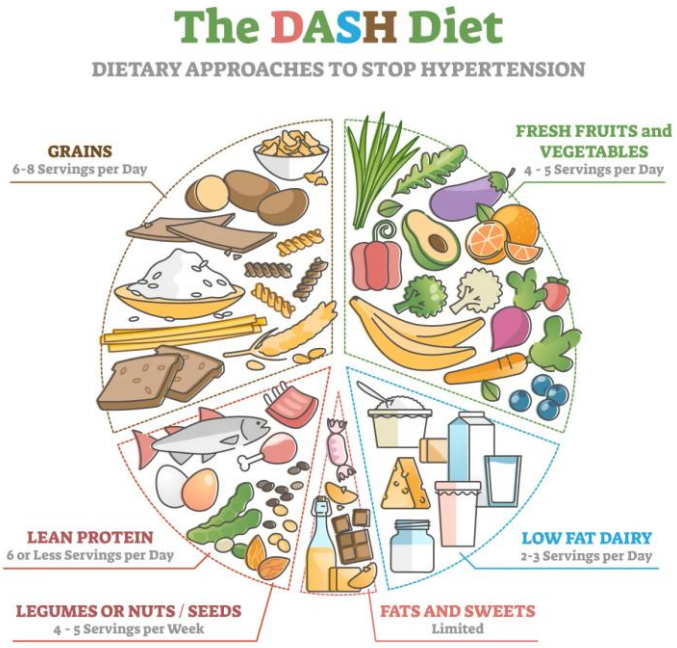
20

DASH Diet

Lowers SBP
11 mmHg in 8 wks

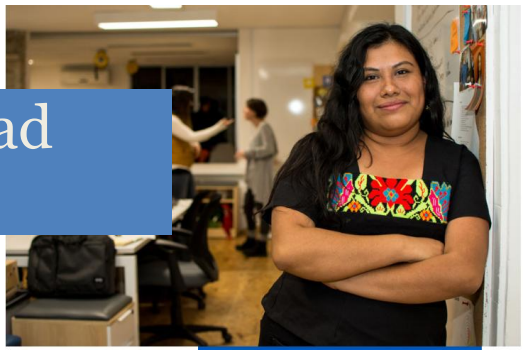
HIGH in Whole Grains, Fruits, Veggies

LOW in Ultra Processed Foods, Salt, Oil, Sugar



21

What If Gaby Had Dyslipidemia?



22

Menopause and Lipids

- Menopause causes abrupt increases in T chol, LDL, and apolipoprotein B levels independent of aging
- Also causes adverse changes in BP and glycemic control during the menopausal transition
- These changes lead to increased risk for metabolic syndrome and CVD in postmenopausal people

23

Lipids and MHT

*effects are less with lower doses

	HDL	LDL	TG	T CHOL
ORAL				
TRANS DERMAL				

24

Lipids and HT

- Consider patient's overall ASCVD risk
- TD estradiol has favorable or neutral effects on lipid parameters and overall CVD risk
  - Progestogens essentially neutral
- Avoid HT in women with pre-existing CVD, otherwise do not hesitate to provide TD estradiol and micronized P

25

Disease-Specific Recommendations

Hyperlipidemia

Reduce

- Trans and saturated fat—hydrogenated vegetable oils, fried foods, commercial baked goods and snack foods, naturally found in meat and dairy (especially cheese and beef), processed meats
- overall meat consumption

Increase

- Poly or monounsaturated fat in place of trans or saturated—omega 3s
- Complex carbs
- Plant sterols and viscous fiber—oatmeal, soybeans, green peas, legumes, avocado, wheat germ, brussels sprouts, almonds, eggplant, okra

26

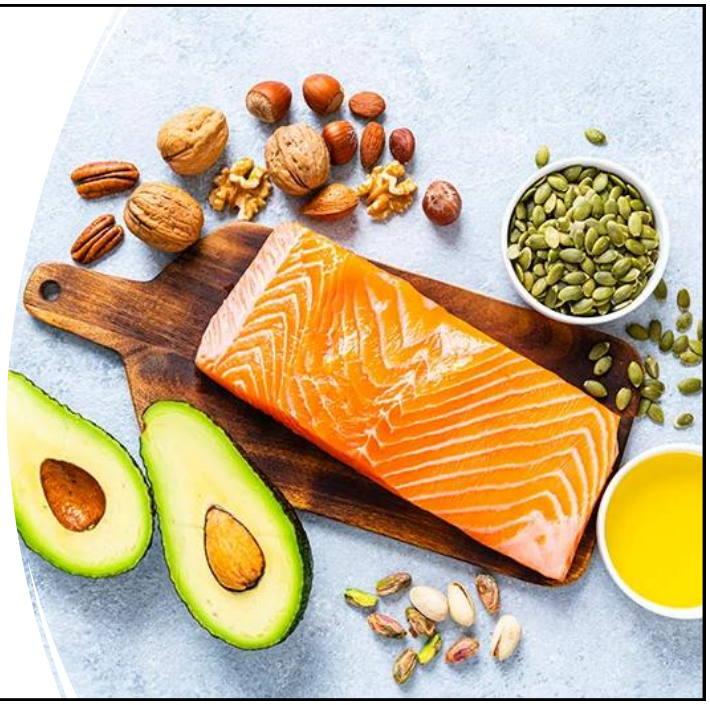
Trans Fat Foods

- Commercial baked goods, such as cakes, cookies and pies
- Shortening
- Microwave popcorn
- Frozen pizza
- Refrigerated dough, such as biscuits and rolls
- Fried foods, including french fries, doughnuts and fried chicken
- Nondairy coffee creamer
- Stick margarine

27

Healthy Fat Foods

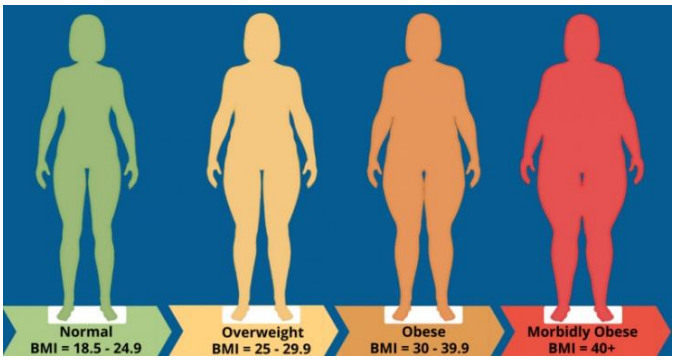
- Polyunsaturated
  - Fatty fish
  - Avocados
  - Nuts and seeds
  - Corn, soybean oil
- Monounsaturated
  - Olive oil



28

Women with BMI >30

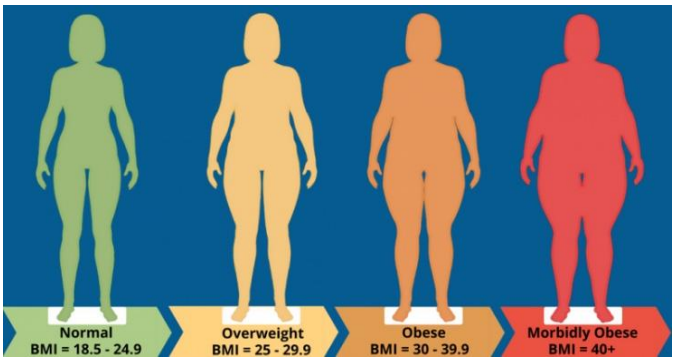
- Weight gain in midlife is primarily related to aging rather than menopause
- Increase in fat relative to muscle
- Decreased resting and active metabolic rate
- Increased visceral fat stores



29

Women with BMI >30

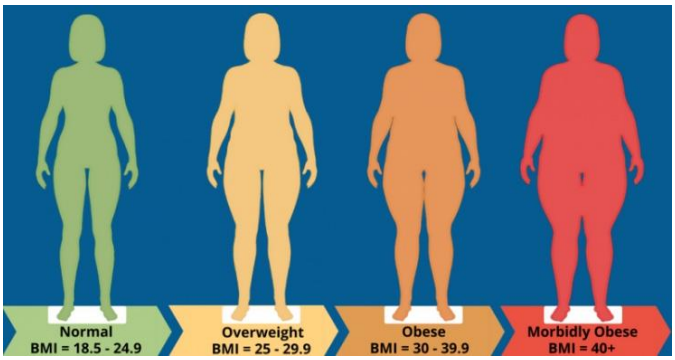
- Avg weight gain after menopause is about 1.5 pounds per year
- Women worry that starting HT will make them gain weight



30

Women with BMI >30

- BMI >30 increases risk for CHD, VTE, breast & endometrial cancers
- ***Obese women more likely to have severe/frequent VMS***



31

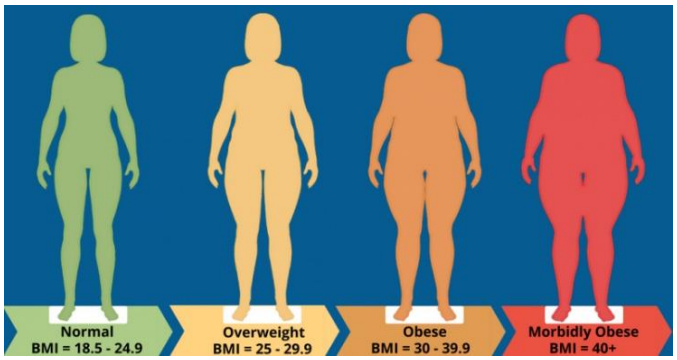
How Does Having a BMI >30 Impact HT Decision Making?

- HT does not help with weight loss ☹
- HT does have favorable effects on body composition and fat distribution
  - Preserves lean body mass
  - Reduces visceral adiposity

32

Recommendation

- Choose transdermal over oral estradiol preparations
- Choose a progestin with lower risk of VTE and minimal effects on metabolic parameters: micronized progesterone (prometrium)
- Advise patients that HT does not cause weight gain
- Provide nutrition prescription



33

NUTRITION PRESCRIPTION:

Core Elements of a Healthy Eating Pattern: **ACLM**

predominantly whole food plant-based diet for disease prevention, treatment, and reversal

AMERICAN COLLEGE OF Lifestyle Medicine

34

Susan: 55-year-old Engineer with T2DM

- Bothersome hot flashes, LMP 2 y ago
- Medical hx:
  - Type 2 DM on metformin
  - Most recent A1C = 7.4
  - No heart disease or stroke history
  - BMI 22
- Vitals, labs, exam are normal

Could she consider HT for treatment of her VMS?

35

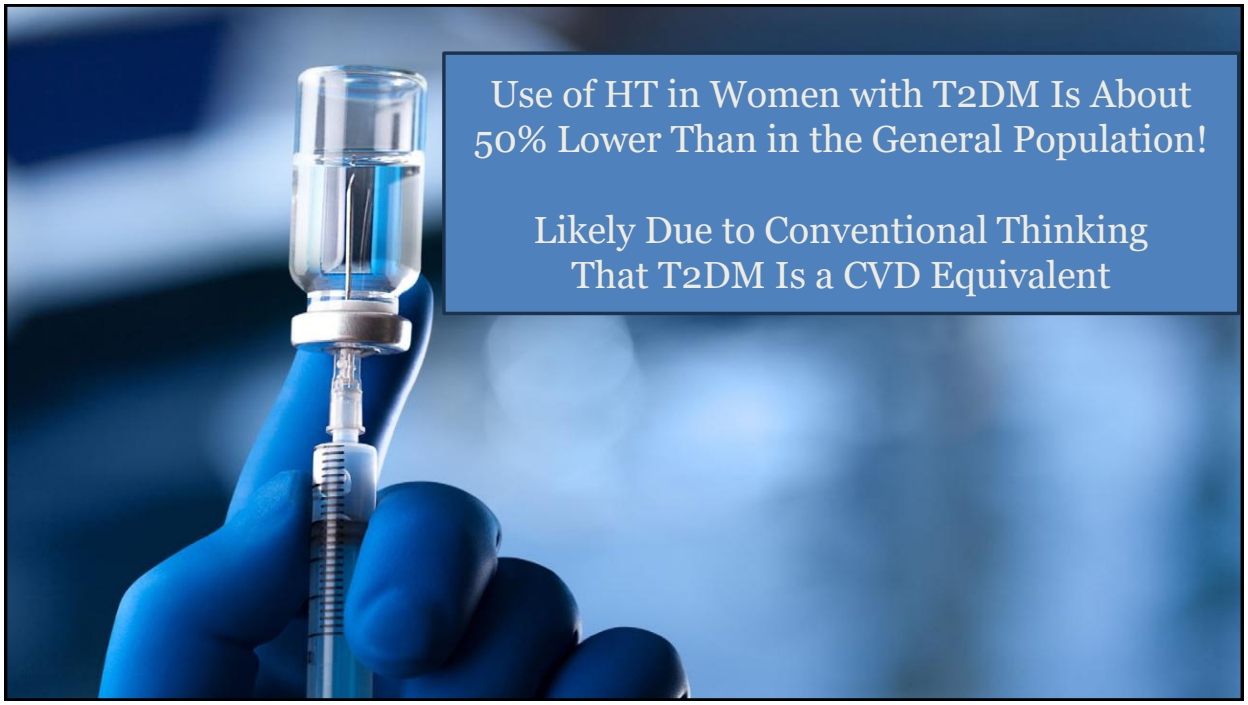
What Would You Offer Susan?

A. Estradiol 0.5 mg/micronized progesterone 100 mg orally (Bijuva)
B. Fezolinetant 45 mg daily
C. TD estradiol 0.05 mg/d biweekly plus micronized progesterone 100 mg nightly
D. Gabapentin 100 mg at bedtime

HT in Women with Diabetes

- HT improves glycemic control and insulin resistance in postmenopausal women *with* and *without* T2DM
- In women with T2DM fasting glucose, lipids, and BP all improved more than in non-diabetic women
  - Lowers visceral adiposity
  - Lowers insulin resistance
  - Improves insulin secretion
- Oral estradiol improves insulin sensitivity more than TD

37



38

HT in Women with Diabetes

RECOMMENDATION:

- Don't avoid HT, but individualize
  - Choose oral ONLY in normal weight women w low CVD risk (rare)
  - TD estradiol in women with obesity or moderate CVD risk
    - lower risk of VTE
    - favorable effects on TG and inflammatory markers
- Micronized progesterone has minimal impact on glycemic control

39

Exercise Prescription for Everyone!

40

Susan

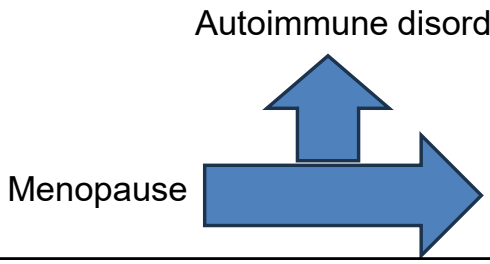
What If Susan Had Systemic Lupus Erythematosus Instead of T2DM?

41

Autoimmune Disorders Common in Women

- Rheumatoid arthritis, SLE, Sjogren's, multiple sclerosis more common in women
  - Second peak in midlife
- Changing estrogen levels may be modifying factor
  - Earlier age at menopause linked w increased risk of SLE, RA, and progression of MS
  - Symptoms of SS may worsen

Hypothesis: a link between menopause & autoimmune disorder risk and course



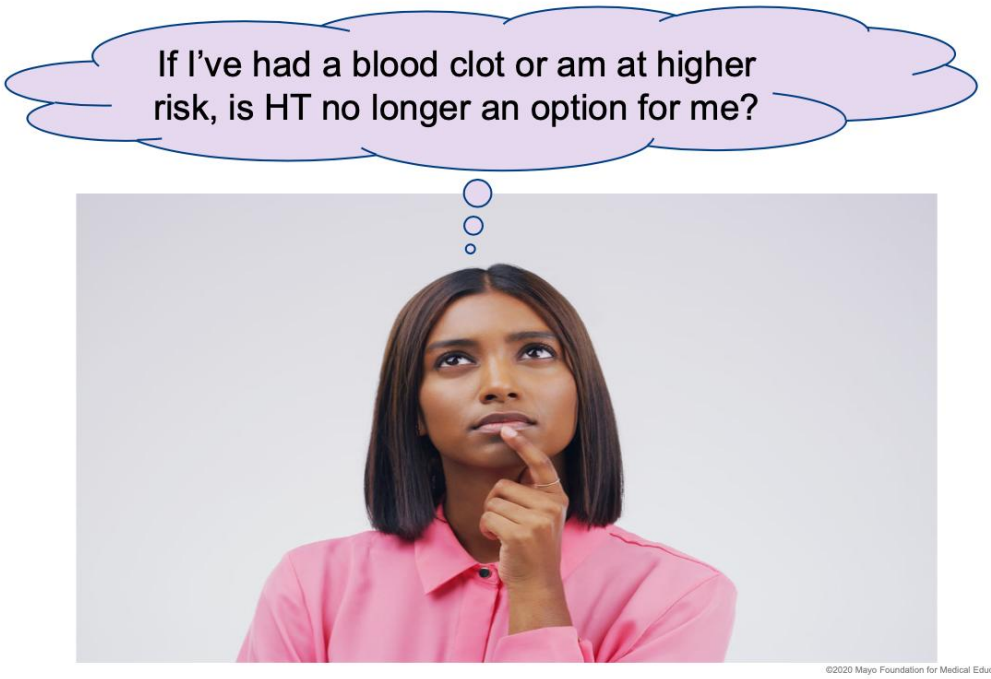
42

Susan: 55-year-old Engineer with SLE

RECOMMENDATION

- Consider HT if no other contraindications
- Avoid oral in:
  - Antiphospholipid syndrome
  - Positive ACA or LA
  - Generally high disease activity
- Data is sparse w Sjogren's
  - Consider vaginal E for genitourinary symptoms

43



44

Women and VTE

- Overall incidence increases with age
  - More than doubles from age 25 to 50
  - 51/100,000/yr to 123/100,000/yr
- Female specific risks: OCPs, pregnancy
- Other risks: obesity, major surgery, trauma, immobility, malignancy, previous VTE, smoking, thrombophilia

45

VTE Risk: Format and Route Matter

- VTE association with use of conjugated equine estrogen (CEE) with or without medroxyprogesterone acetate (MPA)
- There appears to be no such association for transdermal estradiol or for micronized progesterone

46

VTE Risk: Format and Route Matter

- No increased rates of VTE in heterozygous thrombophilias with TD estradiol (F5L)
- **ESTHER:** case-control study (cases were PE/DVT, controls admitted for other causes), median age 62
  - Current use of oral estradiol compared to controls: odds ratio 4.2
  - Current use of TD estradiol compared to controls: odds ratio 0.9

47

VTE Risk: Format and Route Matter

- Type of progestin also influences risk
  - Association of VTE with medroxyprogesterone acetate
  - No association with micronized progesterone

48

Patients with Hx of VTE

Recommendation:

- Consider individual factors
  - Thrombophilia?
  - Provoked/unprovoked?
  - Smoker?
  - QOL/Severity of symptoms
- Review non-hormonal options
- Shared decision making
- Use TD route if estradiol is used and micronized P if progestin is used
- May be considered for symptomatic patients w hx of VTE if anticoagulated

49

Barbara

- 40 yo fitness instructor
- BRCA1+
- Planning RRBSO

50

The Menopause Society: Family History of Breast Cancer

- "Evidence suggests that hormone therapy use does not further increase the relative risk of breast cancer in women with a family history of breast cancer or in women with BRCA 1 or 2 genetic variants"
- "The absolute risk of breast cancer is low in women with genetic variants who undergo risk-reducing BSO at a young age, and use of hormone therapy is considered acceptable."

51

The Menopause Society: Family History of Breast Cancer

- Shared decision making, risks should be assessed when counseling women, factoring risks of early (surgical) menopause into the equation
- BRCA+ women who have undergone RRSO can be provided HT until at least the age of menopause

52

Barbara

- Advise postmenopausal doses of HT at least until age 52
- Evaluate for sexual dysfunction
- Consider local estradiol if needed

53

Maria

- 35 yo attorney
- No period for 15 months
- HCG neg
- TSH, PRL normal
- FSH 59, Estradiol 12
- Neg P withdrawal bleed

54

Early Menopause/POI

- In the absence of contraindications, HT benefits outweigh risks
  - bone
  - heart
  - cognition
  - VVA/sexual function
  - mood
- Start immediately on diagnosis
- Continue at least until avg age of menopause (51)
- Risk of cognitive impairment mitigated by use of HT

55

HT Management in Early Menopause/POI

- Follow estradiol levels, target is 80-120 ng/dL, may need two patches
  - This is the one of the rare times estradiol levels are useful in menopause management
- Consider contraceptive needs
- OCs considered less bone protective than estradiol
- Cannot obtain serum levels with OCs

56

Wrapping Up:

- Data generally supports use of HT in symptomatic women with common medical conditions depending on their overall risk stratification
- Route and dose matter: transdermal and micronized progesterone almost always preferred over oral estradiol and MPA (T2DM might be an exception in rare cases)
- Provide HT to all patients with early menopause/POI at least until age 51
- Everyone should get nutrition and exercise prescriptions!

57

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59