Cardiovascular Considerations in the Perimenopausal and Menopausal Period

Hannah Fish-Trotter, MD
Assistant Professor, UTHSC Cardiology

Ascension
Saint Thomas Heart

Objectives

- Recognize the changing cardiovascular risk profile that accompanies menopause and the menopause transition
- Review current indications for menopause hormone therapy (HT) and replacement hormone therapy for premature menopause
- Identify contraindications and moderate risk factors for hormone therapy to guide shared decision-making conversations
- Discuss the “timing” and “healthy endothelium” hypotheses and why these factors are key to risk-benefit discussions
- Review non-hormonal alternatives

Menopause Transition & Onset

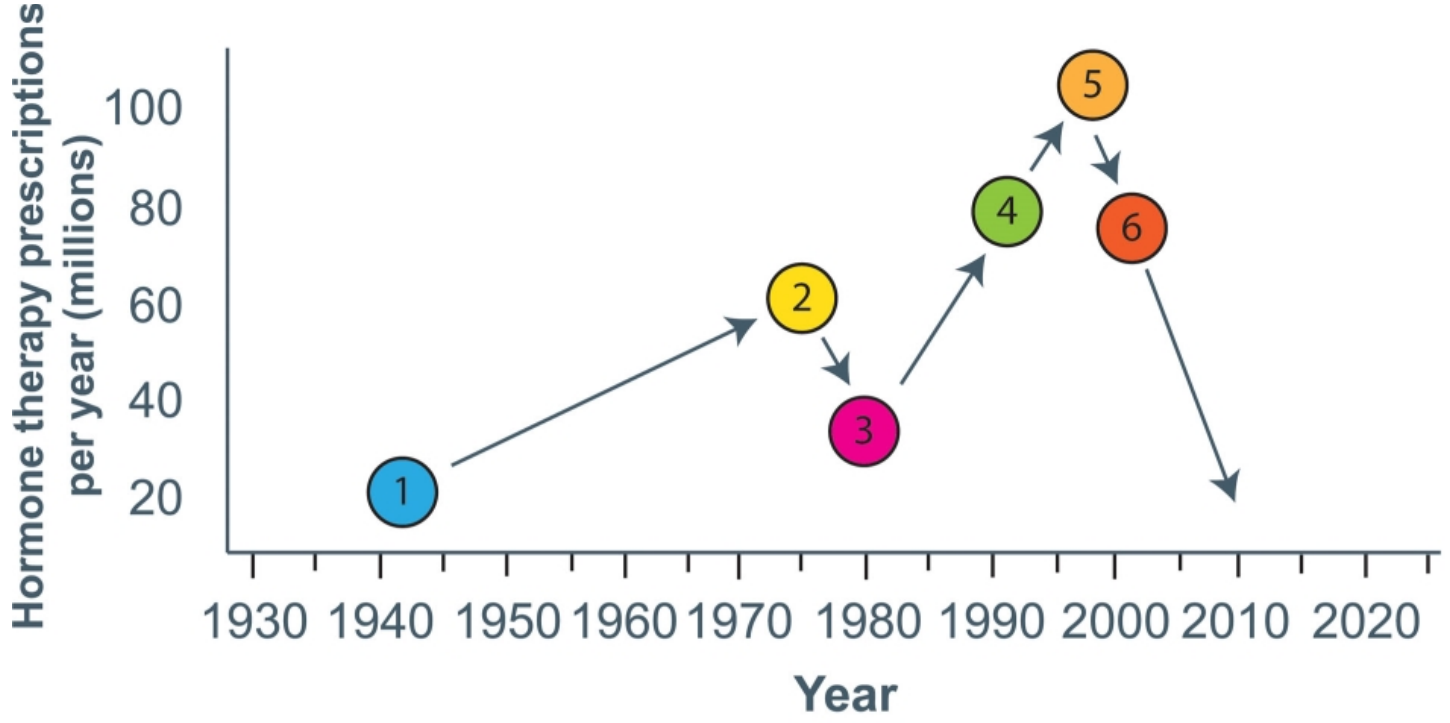
- **Perimenopause** is the transitional period before menopause, characterized by hormone fluctuations, irregular menses and associated symptoms
- **Menopause** onset is defined as 12 consecutive months of amenorrhea
- Average age of menopause onset in the US is **52 years**
- Considered **premature** if before age 40; **early** if onset between 40-45

- **63 million** women in the US over 50 years of age
- **1.3 million** women enter menopause annually in the US
- Women spend **~40% of lifetime** in menopause
- 75% experience **vasomotor symptoms** (hot flashes, night sweats)
- Other symptoms include sleep disturbance, mood changes, anxiety and depression, reduced quality of life

Ascension

Menopause transition: changing cardiovascular risk profile

- Cardiovascular disease is the number one cause of death in women worldwide
- Premenopausal women develop CVD at lower rates compared to age-matched peers
- Menopause transition is a period of accelerated CVD risk per AHA
- Body fat distribution changes with reduced lean mass and increased visceral adiposity
- Increased LDL and lipoproteins
- Increased HDL, but with decreased protective function
- Increased metabolic syndrome, independent of chronological aging
- Increased carotid atherosclerosis, 7.5% increase in arterial stiffness



Timeline

1. 1942: Conjugated equine estrogen first introduced
2. 1975: Endometrial cancer risk recognized
3. 1980: Combined estrogen+progestin introduced
4. 1990s: Nurses' Health Study (1991) + PEPI (1995) published
5. 1998: HERS trial published
6. 2002: WHI trial published

Cho et al, Circulation, 2023

Women's Health Initiative 2002

- RCT, enrolling 160,000 postmenopausal women **aged 50-79 years**
- Randomized placebo versus hormone therapy (conjugated estrogen +/- progestin)
- Initial reports of increased coronary heart disease, stroke, and thromboembolic events in women receiving hormone therapy

→ → HT prescriptions plummeted

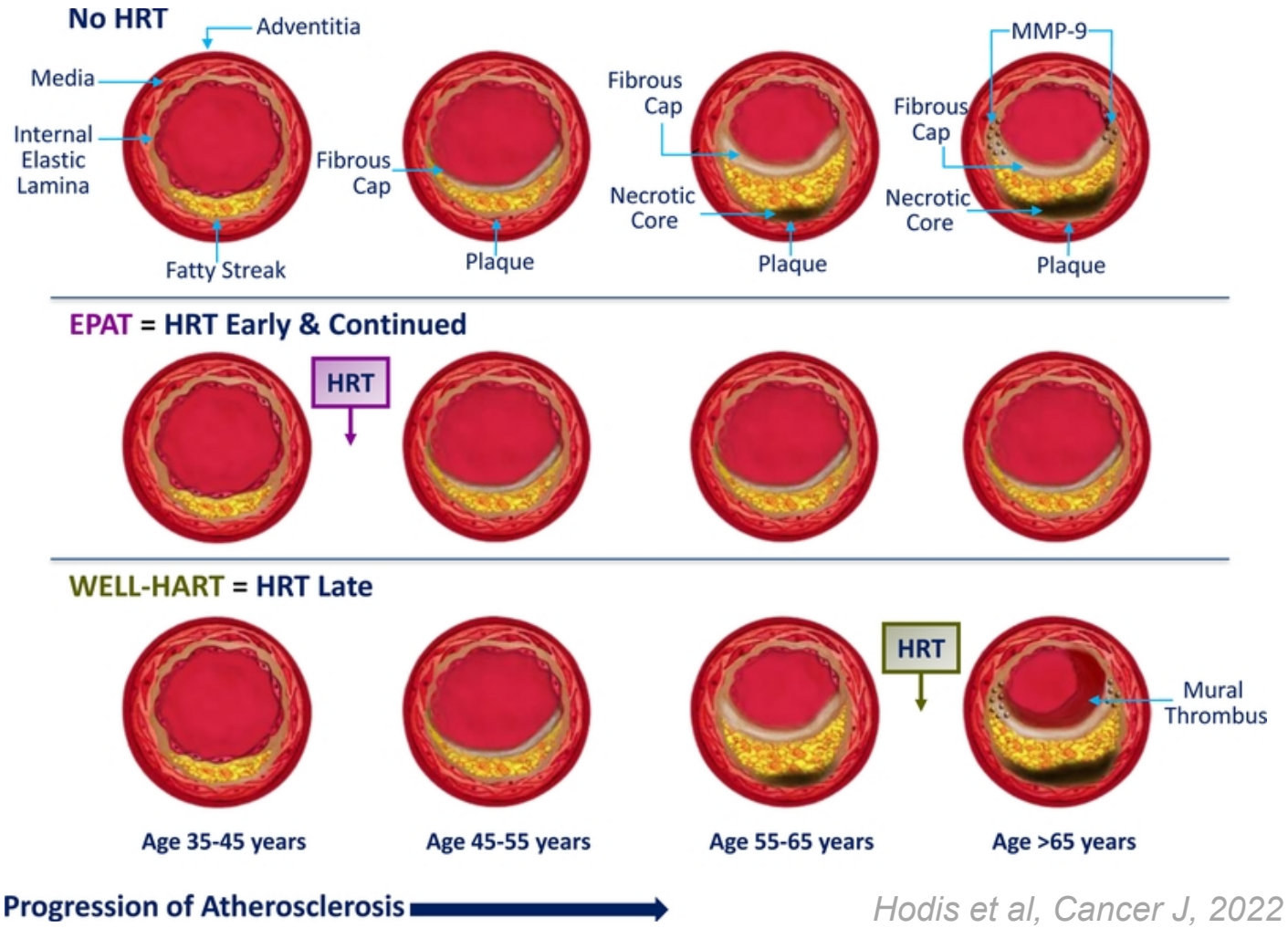
- **Note: median age at time of enrollment was 63 years**
- Age-stratified subanalysis showed the outcomes risk were actually much lower when therapy was initiated between 50-59 years, versus later

→ → "timing hypothesis"

Timing hypothesis supported

- Reanalysis of Nurse's Health Study: reduced CHD risk when HT started earlier
- Danish Osteoporosis Prevention Study (DOPS): mean age 50, HT reduced risk of adverse cardiovascular events by 52%, null effect on stroke risk
- Meta-analyses stratified by age and time from menopause: HT associated with reduced CHF risk and all-cause mortality by 30% when initiated <60 yo or <10 years from FMP
  - → VTE risk was increased (RR 1.74)
- ELITE trial: reduced carotid intimal thickening progression when HT was started in women <6 years from FMP; no benefit when >10 years from FMP

Healthy endothelium hypothesis



Hodis et al, Cancer J, 2022

Premature / early menopause and CVD risk

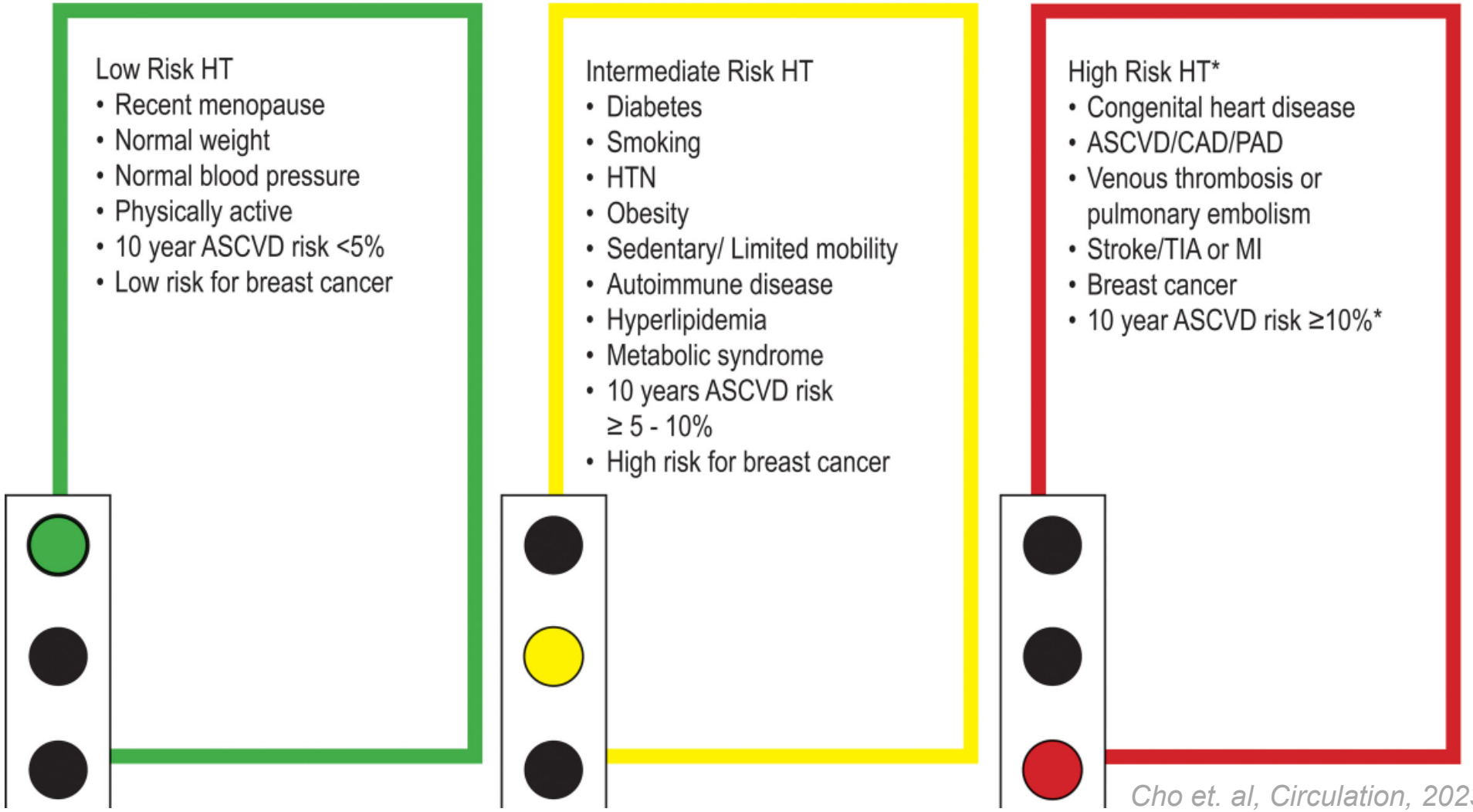
- Early menopause (onset <45 yo) is associated with increased coronary disease (RR 1.5)
- Menopause onset >50 yo is associated with *reduced* coronary disease (RR 0.87)
- Early menopause is associated with increased risk of heart failure (HR 1.33)
- Bilateral oophorectomy at <40yo is associated with increased risk of coronary disease
- CVD risk appears to be the similar among patients with natural premature menopause at age <40yo, compared to surgical menopause at age <40yo

Individualized approach to assessing risk and safety of hormone therapy

- Identify appropriate indications for hormone therapy
- Assess risks and absolute contraindications
- Consider various routes of therapy and non-hormonal options in higher risk patients
- Concurrently, reiterate aggressive optimization of modifiable risk factors

Indications for HT

- **NOT** for primary or secondary prevention of coronary heart disease
- → *except* in the setting of premature menopause (<40yo), whether surgical or physiologic
- YES, for vasomotor symptoms (VMS), including hot flashes, sweats
- Should be considered when <60 years of age *and* within 10 years of final menses
- **VMS are not harmless**; associated with sleep disturbance, reduced QOL
- Meta-analysis: VMS associate with increased coronary disease risk acter adjustment for established CVD risk factors (RR 1.28)
- Poor sleep is associated with metabolic syndrome and increased arterial stiffness
- Depressive symptoms of menopause are linked to increased risk of CVD



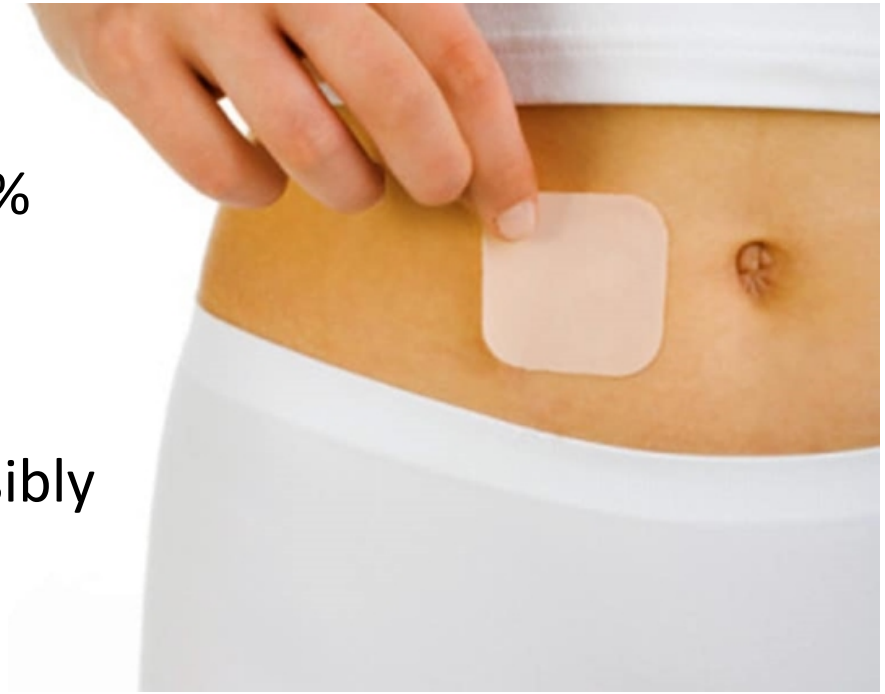
Cho et. al, Circulation, 2023

Systemic therapy

- Associated with LDL lowering, but increased triglyceride levels by 5-15%
- Mixed data on effect on BP, some studies show minimal increase
- Improves glucose control and significantly reduces insulin resistance
- Increased risk of venous thromboembolism

Transdermal therapy

- Associated with triglyceride *lowering* by 5-30%
- Preferred in diabetic patients
- Reduced risk of cardiovascular complications
- Lower risk of venous thromboembolism (possibly due to bypass of first-pass metabolism in the liver)



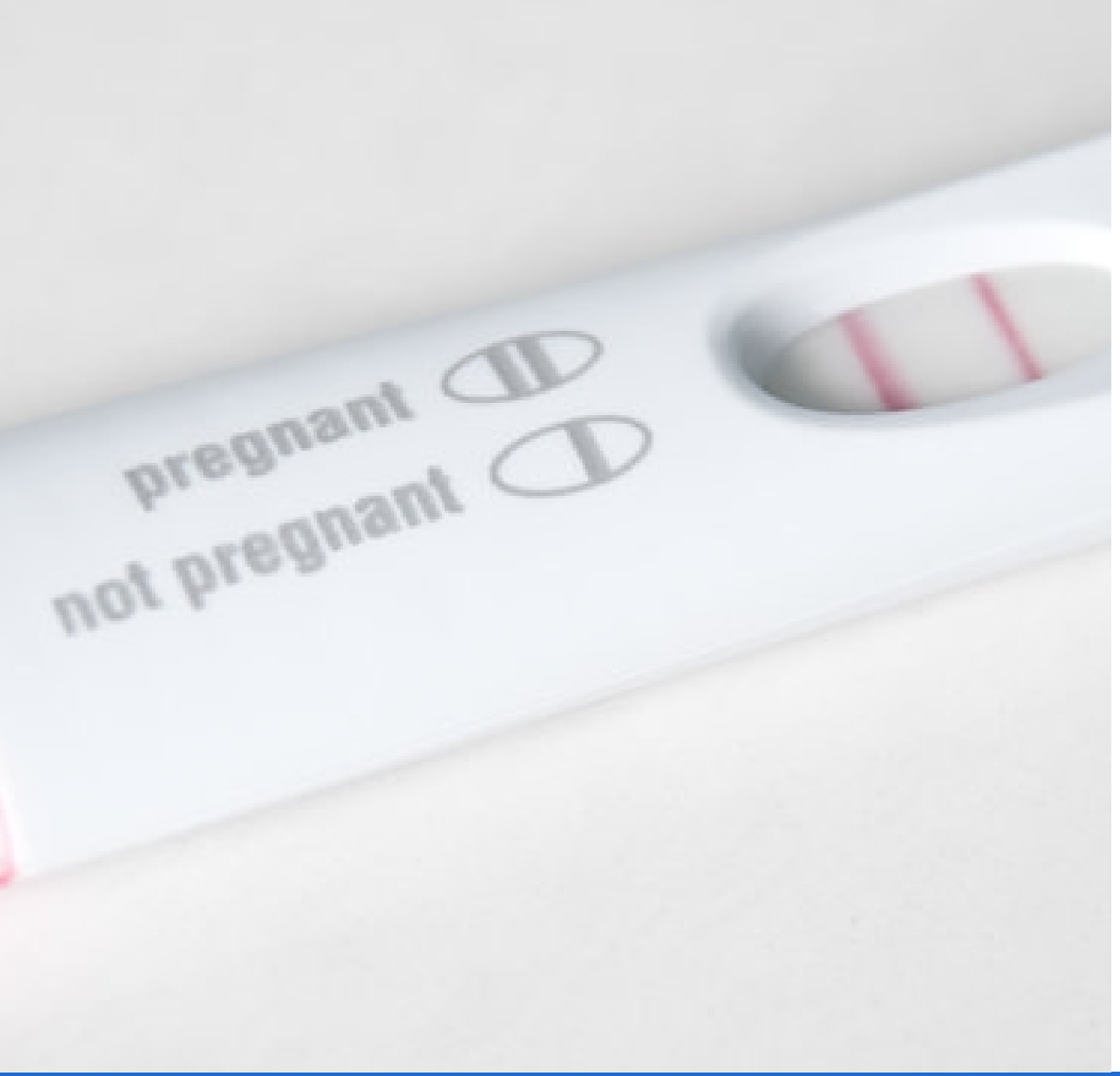
Alternatives options

- Vaginal estrogen cream for GU symptoms
- Non-hormone therapies
  - SSRIs & SNRIs
  - Gabapentin
  - Oxybutynin
  - Neurokinin B antagonists
- Lifestyle measures
  - Weight loss, cognitive behavioral therapy, hypnosis

Modifying CVD risk factors during a period of accelerated risk

- Pittsburgh Women's Health Lifestyle Project – RCT of 535 women, 44-50 yo
  - 5-year intervention with reduced calorie, reduced saturated fat diet and regular physical activity
  - → reduced LDL rise, reduced weight gain, reduced triglycerides and BP across menopause transition
  - → slowed carotid intimal thickening progression across the menopause transition
- Meta-analysis of 59 prospective cohort studies of middle-aged & elderly women
  - Leisure physical activity associates with reduced risk of coronary disease (RR 0.71), stroke (RR 0.77)
  - BMI >30 kg/m^2 associates with increased risk of coronary disease (RR 1.67)
  - Smoking associates with increased coronary disease (RR 3.13), stroke (2.76)

If not already, now is the time for aggressive implementation of lifestyle measures



False + pregnancy test !?!

- During perimenopause and menopause, low levels of hCG may rise along with LH and FSH, secreted by the pituitary in response to reduced estrogen and progesterone, and thus lack of negative feedback
- What to do about periprocedural positive hCG test?
- Hage et al recommend no further evaluation if hCG < 14 mIU/mL and FSH > 40 mIU/mL

Takeaway points

- Menopause transition (perimenopause) is a period of *accelerated* cardiovascular risk
- VMS are not simply a nuisance, and are an indication for HT
- Hormone replacement therapy for **premature** menopause (whether natural or surgical) is associated with reduced cardiovascular risk and should be provided
- HT initiated within 10 years of menopause onset and at <60 yo appears to be associated with cardiovascular benefit, though small increased VTE and stroke risk
- However, primary prevention of CVD is NOT an indication for HT by any medical society (ACOG, NAMS, AACE, Endocrine Society, AHA)
- Assessing appropriateness and safety of HT requires an individualized approach
- Menopause transition period is an opportune time to revisit healthy lifestyle habits

Ascension
Saint Thomas Heart