Learning Objectives

- Physiology of menopausal transition
- Pharmacologic activity of hormone preparations
- Help your patients make based on evidence, risk profile, patients’ preferences
- Women’s Health Initiative 2002
- Controversies re: MHT
- Updated evidence
- Recommendations from professional societies

Defining menopause transition

- Normal physiologic transition (not a medical event)
- Women will live 1/3 of life after menopause
  - No menses x 12 mos; avg age 52
  - Women have the capacity to grow and develop psychologically when viewed as another stage of life, a time of personal reflection and growth
    - Expectation of symptoms
    - Freedom from menses/some sense of loss
    - Changing relationships
    - Status passage / acceptance
Physiology review
- Cycle irregularities
- Fewer follicles, less responsive to FSH
- Ovaries produce less
  - Estradiol
  - Progesterone
  - Androgens
- Negative feedback effect lost, FSH/LH production continues

Physiology review
- Fewer follicles develop
- Ovaries produce less hormone
- Negative feedback effect lost; ant pituitary production of FSH/LH continues
- Irreg cycles
- Symptoms – hot flashes, sleep disruption, vaginal dryness, others

Physiology review
- Follicle production stops
- Est/prog low
- FSH/LH remain high
- Menses stops (12 mos)
- Fluctuating levels in 1st 5 yrs (FSH 40 or +)
- Later – genito-urinary symptoms dominate
- Straw Framework
Menopausal Hormone Therapy

**Indications: FDA approved**
- Treatment of vasomotor symptoms (may take 6+ weeks for noticeable improvement)
  - Hot flashes
  - Night sweats (sleep disruption)
- Vulvovaginal atrophy
- Prevention of osteoporosis

**Contraindications**
- Gall bladder disease
- CHD / stroke
- VTE
- Uterine/ovarian/breast cancer
- Undx genital bleeding
- Pregnancy
- Liver disease
- Breast ca / hx of

Risk profiles to consider

**CV**
- Active smoking
- PM; > 50 yrs
- CRP
- DM
- 1st with MI < 50
- HTN
- Lipid profile

**Breast ca**
- Active smoking
- > 2 etoh/day
- Atypia
- Breast density
- 1st pregnancy > 30
- Risk increases with age

Estrogens

**Oral**
- Conjugated (Premarin)
- Esterified (Menest)
- Estradiol (Femtrace)
- Estropipate (Ogen)
- Synthetic conjugated (Enjuvia)

**Transderm**
- Estradiol (patch, spray, emulsion, gel)

**Vaginal**
- Rings, creams, tablets
- Premarin
- Estring
- Vagifem

**Pharmacologic formulations**
- Human natural (estrone - E, estradiol – 17β, E-2, estriol)
- Non-human (Premarin)
- Phytoestrogens (plant derived)
- Synthetic mixtures (plant or equine derived – Enjuvia, Menest)
- Synthetic analogues (ethyl estradiol – Ortho-Est)
- Pharmacokinetics differ by route
Pharmacologic actions of estrogens

- Highly lipid soluble and rapidly absorbed through skin
- Attach to receptors
- Effects depend on:
  - Relative potency
  - Receptor agonist/antagonist properties
  - Metabolism
  - Route
- Development/maint of female reproductive system
- Secondary sex characteristics
- Skeletal shape – decreases bone resorption
- Urogenital tone/elasticity

Pharmacologic actions of progestins

- Uterus and breast are target organs
- Alters liver function
- Prevents overgrowth of uterine lining but topicals not shown to be effective
- Typically leads to amenorrhea
- Mammographic density increases
- May affect mood
- Must be used in women with uterus (SERMs)
  - Estrogen/BZD – protects against osteoporosis/preservess endometrial ca
  - Osphemphene (oral for dyspareunia)

Progestosterone / Progestin

- Used with/without estrogen (off label use) for VMS
- Side effects – menstrual irregularities, breast tenderness, bloating, headache
- Changing formulations can help manage side effects (from oral to transdermal or IUD)
- Serum levels not studied
- MPA (Provera)
- Micronized progesterone (Prometrium)
- Norethindrone (Aygestin)
Oral vs non-oral

**Oral**
- Preferred by most women
- First pass – liver, higher trig, clotting factors

**Non-oral**
- Eliminates hepatic effect (improves drug levels)
- Fewer GI effects
- Lower rates of VTE, MI, stroke, trig
- Preferred for HTN, HLD
- Vag route better for GUSM
- Preference for non-daily

Duration/discontinuing MHT

- NAMS – has recommended 3-5 years, 7 years or longer may be OK
- IMS – safe at least for 5 years in women < 60 and longer if low risk profile
- Some studies show hot flashes may last 7-10 years
- Re-evaluate periodically; use lowest possible dose for symptom relief
- No evidence to support tapering, but recommended
- If early menopause, then continue to age of normally expected menopause
- Encourage healthy lifestyle

Bioidenticals

**Pharm-FDA approved**
- Estrace
- Micronized progesterone (Prometrium)

**Compounded**
- Personalized preparations
- Safety, effectiveness, claims of superiority unproven
- Less oversight
- No evidence to support saliva testing or blood levels
- Peanut allergy
- Not always covered by ins
Moisturizers and Lubricants

Moisturizers
- Intended for regular use to maintain moisture
- Absorbed into the skin
- May be adequate for intercourse
- Examples:
  - Extra virgin olive oil
  - Vitamin E oil
  - Natural coconut oil
  - Luvena
  - Replens

Use only water soluble products with condoms
If prone to UTI, yeast, or have DM, may not be able to use natural oils

Lubricants
- Intended for use with intercourse
- Astroglide
- I-D Millenium
- K-Y jelly/Kygel
- Liquid Silk
- Lubric
- UberLube
- Replens
- Hypoallergenic:
  - Pink
  - Just like Me
  - Good Clean Love

Women’s Health Initiative 2002
- 1993 – prevention of CVD, breast ca, colorectal ca, osteoporotic fx in pm women
- > 161,000 ages 50-79
- RCT vs observation
  - Estrogen and progestin (CEE and MPA) (Premarin/Provera)
  - Estrogen only (post hyst) (CEE)
- Stopped E/P arm after 5.2 yrs
  - CVD: 1.29 (HR)
  - Br ca: 1.26 (HR)
  - Stroke 1.41 (HR)
- Colo: 0.63 (HR)
- End ca: 0.83 (HR)
- Hip fx: 0.66 (HR)

Effects of WHI
- Changed US practices overnight
- Decreased use of all types of HT by ½
- Estimated to saved $ 35.2 billion
- Spawned ~ 300 additional studies, 1400 pubs
- Many women changed to bioidenticals, compounded formulas
Hormone Therapy for Primary Prevention of Chronic Conditions in Postmenopausal Women:

PM women: The USPSTF recommends against the use of combined estrogen and progestin for the primary prevention of chronic conditions in postmenopausal women.

PM 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: The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. Discourage the use of this service.


Evidence Grading - USPSTF

A: High certainty of substantial benefit: Offer service

B: High certainty that net benefit is moderate: Offer service

C: Moderate certainty that net benefit is small: Offer selectively

D: Moderate or high certainty service has no net benefit or harms outweigh benefits: Discourage use

I: Insufficient evidence: If offered, patients should understand uncertainty of benefits vs risks

Questions

1 – are PM women who use HT at decreased or increased risk of morbidity / mortality (stroke, cancer, VTE, fracture) when compared with PM women who do not use hormone therapy?

2 – Does age and time since menopause influence morbidity and mortality factors in PM women?

Databases: PubMed, Scopus, NG Clearinghouse
Evidence – 2017

Issues of debate:
- Timing of initiation of MHT
- WHI not intended, not statistically powered to evaluate use near menopause
- All E/P hormones not the same
- USPSTF – overreaching conclusions having significant public health impact

Who?
- NAMS
- IMS
- ACOG
- Endorsed by 30 US and international organizations

*** Studies that have continued to follow women who began MHT near menopause, with long term use, continue to show benefits for prevention of CHD, fracture and dementia*****

Menopause, 24(10);2017:1101-1112

Specific risks

Breast cancer
- HR: 1.20 (95% CI, 0.94-1.53) – E/P
- Not significant
- Evidence that other types of progestins do not cause breast ca

VTE/Stroke
- Sites only oral meds
- No increased risk when non-oral meds used
- No increased risk of stroke for women 50-59 in MHT arm

Specific risks

Cognitive impairment
- 65 and older
- Elite Trial – MHT c/w placebo – no effect on cognition whether beginning in 6 yrs of or 10 years after menopause
- Transderm + Intermittent MP prevented symptoms of clinical depression in early menopausal women

Neurology 2016;87:699-708

JAMA Psychiatry, pub online 1/10/18

Fracture
- Osteoporosis – chronic disease with tremendous impact in pm women
- Globally, MHT is approved for prevention of osteoporosis
- Estrogen facilitates normal architecture vs bisphosphonates (excess mineralization)
Specific risks

Urinary Incontinence/GSM
- > 50% PM women
- GSM responds well to estrogen – vaginal, transdermal, oral
- Treatment continues to prevent recurrence
- Therapeutic standard
- Important QOL issue

Cardiovascular
- CVD – leading cause of death / public health problem
- E alone – decreases mortality by 30-40%, maybe by 50% in younger women
- In MHT – 18-54%
- Lifestyle interventions decrease mortality by 12-14%

Maturitas 2016;83:40-44

Summary Updated Evidence - 2018
- HT is appropriate for younger women in early menopause for treatment of menopausal symptoms due to improved QOL which outweighs rates of adverse events
- Women who start MHT near menopause continue to show benefits for prevention of CHD, fracture, dementia, GSM – underlying mechanisms to be determined
- Younger (peri and early pm) women have lower rates of CVD, blood clot and stroke
- Individualize therapy

Language matters - Thank you!

Preferred
- Menopausal hormone therapy
- GUSM
- Alteration in sexual satisfaction

Unfavorable
- Hormone replacement
- Vulvovaginal atrophy
- Sexual dysfunction
- Woman unfriendly terms: "dys;" "atrophic;" "non-compliant" 27
References


