Menopause is a “living decay in which women descended into a vapid cow-like state. Supplemental estrogen would almost magically transform the dull cow into a supple, younger-looking wife and mother. She would not only feel better but also make those around her feel better—especially her partner in bed.”

MANAGEMENT OF MENOPAUSAL SYMPTOMS

<table>
<thead>
<tr>
<th>Menopause</th>
<th>Pre-menopause</th>
<th>Late Perimenopause</th>
<th>2 years Post menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of energy</td>
<td>43</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Depression</td>
<td>26</td>
<td>38</td>
<td>32</td>
</tr>
<tr>
<td>Aches and joint pain</td>
<td>41</td>
<td>53</td>
<td>57</td>
</tr>
<tr>
<td>Insomnia</td>
<td>31</td>
<td>38-39</td>
<td>43</td>
</tr>
<tr>
<td>Memory change</td>
<td>31</td>
<td>44</td>
<td>42</td>
</tr>
<tr>
<td>Vasomotor</td>
<td>10</td>
<td>42-58</td>
<td>41-48</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>3</td>
<td>21</td>
<td>32</td>
</tr>
<tr>
<td>Bladder control</td>
<td>12</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>42</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>18</td>
<td>23</td>
<td>29</td>
</tr>
</tbody>
</table>

Facing a Clinical Dilemma

DEPRESSION

Depressed
Irritable
Anhedonia
Thoughts of death
Worthlessness

MENOPAUSE

Hot flushes
Concentration
Sleep
Weight change
Libido

Energy

Thoughts of death
Worthlessness

Why Consider Hormone Therapy?

HT is the most efficacious therapy for VMS

Cochrane database review showed

– 75% reduction in frequency for any HT
– Significant reduction in hot flash severity
– Combination of E+P slightly more effective than E alone

• Progestin alone has also demonstrated some efficacy

Why bioidenticals?

• Response to 2002 WHI and suspicion of traditional medicine
• Perception of safer alternative
  – fear of cancer (especially breast cancer) and traditional HT
• Patients still having symptoms
• Wider advertising and broad availability (e.g., Internet)
• Patient comfort with alternative medicines

Efficacy of HT vs. Herbals, Soy and Botanicals

Best evidence

Pharmaceutical standardized products

• 17β-estradiol – oral and transdermal via patch or gel
• Micronized progesterone in peanut oil

Compounded with prescription by physician for pharmacist

• Customized estrogen mixtures of 80-90% estriol with 10-20% estradiol (Bi-Est) – 1.25 and 2.5 mg
• Older Tri-Est contained 80% estriol, 10% estradiol and 10% estrone

What is available for women?
**Non-hormonal Medications for VMS**

**Gabapentin**
- 600 mg HS for night sweats
- 600-2400 mg/d in 3 divided doses
- Effective for VMS, no impact on mood
- Side effects in 25% of women (headache, dizziness, disorientation)

**Clonidine**
- Mildly effective at 0.05-0.075 mg bid
- 12% report reduction of >75%
- Most common side effects: dry mouth, constipation, fatigue, restless sleep

**SSRI/SNRI**
- Dosage depends on SSRI/SNRI
- Most studied in breast cancer survivors
- Variable improvements (up to 79% reduction in VMS)
- Reduction in severity and frequency

---

**Overall Benefits of HT**

**Demonstrated efficacy:**
- ↓ Vasomotor symptoms
- ↓ Urogenital atrophy
- ↓ Somatic pain, arthralgia
- ↓ Risk of osteoporotic fractures
- ↓ Risk of colorectal cancer
- Mood stabilization

---

**Risk/Benefit Analysis from Hormone Therapy Trials**

<table>
<thead>
<tr>
<th>Clinical Event</th>
<th>HERS (E&amp;P)</th>
<th>WHI (E&amp;P)</th>
<th>WHI (E Alone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>0.99</td>
<td>1.29*</td>
<td>0.91</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.23</td>
<td>1.41*</td>
<td>1.39*</td>
</tr>
<tr>
<td>PE</td>
<td>2.79</td>
<td>2.13*</td>
<td>1.34</td>
</tr>
<tr>
<td>Breast CA</td>
<td>1.30</td>
<td>1.26*</td>
<td>0.77</td>
</tr>
<tr>
<td>Colon CA</td>
<td>0.69</td>
<td>0.63*</td>
<td>1.08</td>
</tr>
<tr>
<td>Hip Fracture</td>
<td>1.10</td>
<td>0.66*</td>
<td>0.61*</td>
</tr>
<tr>
<td>Death</td>
<td>1.08</td>
<td>0.98</td>
<td>1.01</td>
</tr>
<tr>
<td>Global Index</td>
<td>...</td>
<td>1.15</td>
<td>1.01</td>
</tr>
</tbody>
</table>

* Statistically significant

---

**Contraindications to HT**
- Unexplained/undiagnosed vaginal bleeding prior to investigation
- Known or suspected breast carcinoma
- Acute liver disease
- Active thromboembolic disease
- Acute cardiovascular disease
- Recent stroke
- Pregnancy

**Non-contraindications to HT**
- Smoking
- Diabetes
- Hypertension
- Migraine

---

**Case Study # 2**

- A 36-year-old teacher with premature menopause with complaints of hot flashes and night sweats that are interfering with her sleep and work.
- She previously underwent a total hysterectomy with bilateral oophorectomy for the treatment of severe pelvic inflammatory disease and tubal abscesses.
- After 6 months of oral estrogen, continued VMS, fatigue, decreased energy and libido.

---

**Premature Menopause**

- Medically a distinct group
- ↑ risk of negative effects on cardiovascular system, bone, cognition, mood & sexuality
Biological Potency Oral Contraception vs. Hormone Therapy

The biological potency of oral contraceptives is 3 to 5 times that of Hormone Therapy.

Hormonal Contraception

Reproductive Age

Hormone Therapy

Impact of Age on CV Risk from HT

Data from Multiple RCTs

Younger Women < 60

Older Women > 60

WHI Re-analysis: Effect of Estrogen Alone on Major Outcomes for Women <60 Years vs 70-79 Years

Differences in Outcomes in Women Who Received CEE*

<table>
<thead>
<tr>
<th></th>
<th>50-59 Years</th>
<th>70-79 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute MI</td>
<td>-12</td>
<td>+16</td>
</tr>
<tr>
<td>Death</td>
<td>-13</td>
<td>+19</td>
</tr>
<tr>
<td>Adverse events</td>
<td>-18</td>
<td>+48</td>
</tr>
</tbody>
</table>

*Expressed as absolute rates per 10,000 women annualized over the average follow-up period of 10.7 years

Atherosclerosis timeline: A unifying hypothesis

Case Study # 3

- 54 years old, BMI 32, postmenopausal (2 years since her last menstrual period).
- Family history of stroke (Dad) and DVT (Mom).
- She is experiencing disruptive menopause symptoms including night sweats, hot flashes and severe moodiness. These were initially self-managed with herbal remedies, but her symptoms are now having a more severe impact on her life (e.g., increased work absences, frequently upset and irritable).
- She is worried about the risk of VTE associated with hormone therapy and feels it is too risky for her.
Risk Factors for VTE

- Increasing age
- Obesity body mass index over 30
- Previous VTE
- Post-thrombotic syndrome
- Varicose veins with phlebitis
- First degree family history of VTE
- Immobility for more than 3 days
- Surgical procedures
- Other disorders

Duration of HT Use and VTE

<table>
<thead>
<tr>
<th>Year</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>4.01</td>
</tr>
<tr>
<td>Year 2</td>
<td>1.97</td>
</tr>
<tr>
<td>Year 3</td>
<td>1.74</td>
</tr>
<tr>
<td>Year 4</td>
<td>1.70</td>
</tr>
<tr>
<td>Year 5</td>
<td>2.90</td>
</tr>
<tr>
<td>Year 6</td>
<td>1.04</td>
</tr>
</tbody>
</table>

Why Transdermal? Why Now?

- Needs assessment revealed gaps in practitioner knowledge
- Extensive information on oral hormone therapy; only delivery system looked at in WHI
- Since then – information has continued to evolve over past 10 years
- New science on transdermal delivery system
- There is a difference

Case Study # 4

- 49 year-old P-0 woman whose last menstrual period was 3 months ago.
- Her mother is a breast cancer survivor.
- History of DVT from 20 years ago
- She presents reporting difficulty sleeping because of hot flushes. She feels that this is interfering with her ability to function. She also reports that she has no energy.
- She currently smokes (1/2 pack per day).
- She has dense breasts on mammogram.
Transdermal Estrogens: Impact on Cardiovascular Risk Factors

- Estrogen and Thromboembolism Risk (ESTHER) study.2
  - Lower risk of VTE compared with oral E2
- Markers of inflammation unaffected2
- Triglycerides decreased3
- Less effect on SHBG and TBG
- Less favourable for HDL and LDL changes4, CEE alone and CEE + MPA have a favourable effect on HDL-C
- Decreased CV risk in patients with metabolic syndrome5, 7

SHBG = sex hormone-binding globulin; TBG = thyroxine-binding globulin.

Some Postmenopausal Women are at Higher Risk of VTE

<table>
<thead>
<tr>
<th>Risk (odds ratio)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>3.4</td>
</tr>
<tr>
<td>Prothrombin mutation</td>
<td>4.8</td>
</tr>
<tr>
<td>Oral E</td>
<td>3.2</td>
</tr>
<tr>
<td>Transdermal E</td>
<td>1.0</td>
</tr>
<tr>
<td>Prothrombotic mutation + oral E</td>
<td>25.5</td>
</tr>
</tbody>
</table>

Oral, but not transdermal, estrogen increased VTE risk in postmenopausal women with prothrombotic mutations


HORMONE THERAPY AND RECURRENTITY OF VENOUS THROMBOEMBOLISM

- 1,023 postmenopausal women with a confirmed first VTE were followed for risk of recurrence and impact of HRT
- Recurrent VTE occurred in 77 women
- Transdermal estrogens H.R. 1.0
- Oral estrogens H.R. 6.4
- Progestogen use was not significant

Risk of VTE with Oral vs. Transdermal Estrogen: The ESTHER Study

Hazard ratios of idiopathic VTE in relation to both estrogens by route of administration and concomitant progestogens

<table>
<thead>
<tr>
<th></th>
<th>Age-adjusted HR</th>
<th>Multivariate adjusted HR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never use (n=181)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Past use (n=46)</td>
<td>1.0 (0.7-1.3)</td>
<td>1.1 (0.8-1.5)</td>
</tr>
<tr>
<td>Current use of oral estrogens (n=94)</td>
<td>1.5 (1.0-2.3)</td>
<td>1.7 (1.1-2.4)</td>
</tr>
<tr>
<td>Current use of transdermal estrogens (n=76)</td>
<td>1.1 (0.7-1.4)</td>
<td>1.1 (0.8-1.8)</td>
</tr>
</tbody>
</table>

*Adjusted for age, body-mass index, parity, educational level and time-period.

Endo 2006;91(8):3123

Postmenopausal HT and Risk of VTE: Results of the E3n Trial

<table>
<thead>
<tr>
<th></th>
<th>Crude HR</th>
<th>Adjusted HR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (n=14,986)</td>
<td>1.00 [reference]</td>
<td>1.00 [reference]</td>
</tr>
<tr>
<td>Transdermal route (n=103)</td>
<td>0.62 (0.34-1.14)</td>
<td>0.95 (0.47-1.92)</td>
</tr>
<tr>
<td>Low dose ≤50 mg (n=76)</td>
<td>0.78 (0.46-1.33)</td>
<td>0.81 (0.42-1.60)</td>
</tr>
<tr>
<td>High dose &gt;50 mg (n=27)</td>
<td>1.87 (1.17-3.00)</td>
<td>1.89 (1.15-3.31)</td>
</tr>
<tr>
<td>Oral route (n=619)</td>
<td>1.20 (0.93-1.55)</td>
<td>1.28 (0.95-1.72)</td>
</tr>
<tr>
<td>Low dose* (n=115)</td>
<td>1.16 (0.84-1.61)</td>
<td>1.25 (0.87-1.78)</td>
</tr>
<tr>
<td>High dose* (n=103)</td>
<td>1.51 (1.02-2.20)</td>
<td>1.48 (1.03-2.13)</td>
</tr>
</tbody>
</table>

*Adjusted for age, body-mass index, smoking status, alcohol intake, diabetes, hypertension, arterial fibrillation, CVD, history of stroke or transient ischaemic attack, age or other VTE risk, and history of hyperlipidemia or hypercholesterolemia.

Chu MC. Metabolic syndrome in postmenopausal women: the influence of oral or transdermal estradiol on inflammation and coagulation markers. Am J Med 2002;113(4):331


Lewandowski KC. Effects of hormone replacement therapy type and route of administration on plasma matrix metalloproteinases. J Clin Endocrinol Metab 2008;93(3):922-926


Estrogen Therapy: Smoking Impacts Selection of Route of Administration

**Smoking**
- Free E₂ levels may be lower in smokers (↑ liver metabolism; ↑ sex-hormone-binding globulin)\(^1,2\)
- Increased dose of oral E may be required
- Transdermal E may be beneficial

**Available Progestogens**
- Micronized progesterone (natural)
  - Prometrium\(^*\)
  - Chemically identical to endogenous progesterone
  - Only natural agent approved by Health Canada & U.S. FDA for oral use
- Synthetic progestins
  - C-21 class (e.g., medroxyprogesterone acetate)
    - e.g., Megestrol\(^*\), Provera\(^*\)
  - 19-nortestosterone class (e.g., norethindrone acetate)
    - e.g., Micronor\(^\text{®}\), Norlutate\(^\text{®}\)

**Micronized Progesterone Metabolism**
- Metabolized primarily by the liver
- Metabolites act at non-sex-steroid receptor sites
- Beneficial effects of metabolites
  - Sedation effect with higher doses of oral progesterone
  - Has anti-aldosterone properties
    - May reduce bloating, breast tenderness and edema
- Adverse effects of metabolites
  - May cause nausea and dizziness
  - Contraindicated in patients with peanut allergy

**Progestogen Indications**
- Primary menopause-related indication is endometrial protection from unopposed ET
- Not necessary with standard doses of vaginal ET (including vaginal ring)
- Progestogen not generally indicated with ET post-hysterectomy

**Case Study # 5**
- 52 years old, 2 years postmenopausal. Currently experiencing severe VMS, sleep deprivation, decreased libido and sexual response, and dyspareunia.
- Has experimented with black cohosh with no success. Trials of clonidine and venlafaxine also resulted in a poor response.
- Patient is interested in trying HT but does not wish to experience BTB and has family hx of breast cancer
- She currently smokes 1/2 pack per day.
Risk Factors for Breast Cancer

Relative Risk

- 2 affected relatives
- Obesity
- Young menarche
- HRT 5 years
- 1st child age 30
- 1 year post HRT
- 5 years post HRT
- Alcohol
- Exercise
- Menopause <48
- 10 years app

Breast Cancer Risk and Progestogen Selection

Relative risk of invasive breast cancer by type of HT and duration of exposure, compared with HT never-use

<table>
<thead>
<tr>
<th>Type of HT</th>
<th>Adjusted relative risk* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen alone (n=20,347)</td>
<td>1.29 (1.02-1.65)</td>
</tr>
<tr>
<td>Estrogen + progestrone (n=40,337)</td>
<td>1.00 (0.83-1.22)</td>
</tr>
<tr>
<td>Estrogen + dydrogesterone (n=31,045)</td>
<td>1.14 (0.96-1.34)</td>
</tr>
<tr>
<td>Estrogen + other progestogens (n=104,243)</td>
<td>1.69 (1.50-1.91)</td>
</tr>
</tbody>
</table>

N=80,377 postmenopausal women, mean age 52.4 years. At start of HT, 31.9% of participants were aged 40-45 years; 25.7% were 45-50 years, 20.4% were 50-55 years, 13.8% were 55-60 years, and 8.2% were 60-65 years.

Adjusted for time since menopause, age at menarche, parity and age at first full-term pregnancy, breastfeeding, age at menopause, type of menopause, personal history of benign breast disease, family history of breast cancer in first-degree relatives, family history of breast cancer in other relatives, BMI, previous mammography. Further stratified on year of birth.


PEPI: Effects of HT on HDL-C in Post-Menopausal Women

Average Changes in HDL – Baseline to 36 Months

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>CEE*</th>
<th>CEE + MP* cyclic</th>
<th>CEE + MPA cyclic</th>
<th>CEE + MPA continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Placebo
CEE* = conjugated equine estrogen; MP = micronized progesterone; MPA = medroxyprogesterone acetate.
P < 0.001 for all active treatment groups.
*P < 0.004 for CEE, CEE + MP cyclic.

Investigators’ Evaluation of Sleep Efficiency: Micronized Progesterone vs. Hypnotics

Micronized progesterone can produce an effect similar to that of hypnotics with respect to sleep efficiency improvement without:
- modifying normal sleep architecture
- inducing daytime sleepiness

Improved Sleep Efficiency as a Benefit of HT

Fragmented sleep
A source of:
- daytime fatigue
- loss of concentration
- psychomotor performance
- mood changes

“Better sleep”
Often reported by women as one of the most important benefits of HT

Sexual Health

- Sexual health is important to quality of life at any age
- Majority of women age 50+ sustain sexual interest and ability into old age
- Sexuality of the older woman is an important medical concern

GUIDELINE RECOMMENDATIONS FOR THE MANAGEMENT OF MENOPAUSAL SYMPTOMS

- Estrogen Therapy, with or without a progestogen, is the most effective treatment for menopausal-related vasomotor symptoms
- Individualization of therapy is key
- Low absolute risk potential for Hormone Therapy
  - "Growing body of evidence that each type of estrogen and progestogen, route of administration and timing of therapy has distinct beneficial and adverse effects."
- Further research essential

SOGC Consensus Recommendations 2009 Update

- Menopause is a major life transition with opportunity for healthy interventions
- Patient concerns may be related to aging as well as menopause specific
- Primary indication for HT:
  - Management of moderate to severe menopausal symptoms (Grade A)
- HT should not be prescribed for primary or secondary prevention of:
  - Cardiovascular disease
  - Primary prevention of dementia (Grade A)

SOGC Consensus Update 2009: Dose and Duration of HT

- Appropriate route and dose, according to symptoms
  - Vaginal preferred for vaginal symptoms only
- HT should be prescribed at the appropriate dose and duration to achieve treatment goals
- Prolonged treatment may be offered with appropriate assessment and counselling

NAMS Position Statement 2010

- Estrogen Therapy, with or without a progestogen, is the most effective treatment for menopausal-related vasomotor symptoms
- Individualization of therapy is key
- Low absolute risk potential for Hormone Therapy
  - "Growing body of evidence that each type of estrogen and progestogen, route of administration and timing of therapy has distinct beneficial and adverse effects."
- Further research essential
Endocrine Society Scientific Statement on HT

- Overall mortality: Menopausal HT (MHT) was associated with a 40% reduction in mortality in trials in which participants had a mean age below 60 yr or were within 10 yr of menopause onset.
- Standard-dose oral MHT may increase stroke risk by about 1/3 in generally healthy postmenopausal women.
- Transdermal estrogen does not increase venothrombotic episode risk.
- Micronized progesterone in combination with estrogen does not increase breast cancer risk if given for 5 years or less.


The Medical Letter Position BHT

“There is no acceptable evidence that “bioidentical” (custom-compounded) hormones are safe or effective. Patients should be discouraged from taking them.”

May 2010

Summary

- Primary purpose for prescribing HT remains symptomatic relief
- Transdermal estrogens are considered part of the armamentarium of HT
  – May offer certain benefits in specific clinical scenarios
- Micronized progesterone may also offer benefits in bleeding patterns and reduced risk of breast cancer compared to MPA
- Evidence-based recommendations for management of menopausal symptoms can help guide optimal treatment decisions

SOGC Trusted Resources

- sogc.org
- menopauseandu.ca
- endometriosisinfo.ca
- sexualityandu.ca
- hpvinfo.ca

Question # 1

A 53-year-old patient continues to complain of low libido. She has had a simple hysterectomy for fibroids in the past, and her menopausal symptoms are now well controlled using a daily dose 1 mgm of micronized estradiol p.o. You have taken a sexual history and provided appropriate counseling. Which of the following would you consider, if any?

1. Obtain serum levels of total, free and bio-available testosterone
2. Obtain levels of SHBG
3. Start transdermal testosterone therapy
4. Change from oral to trans-dermal estrogen therapy
5. Start oral androgen therapy
6. Maintain status
7. All of the above

Question # 2

Which one of the following regimens would be considered “bio-identical”?

1. Transdermal estradiol and oral micronized progesterone
2. Combination estradiol norethindrone acetate patch
3. Transdermal estradiol patch and levonorgestrol IUD
4. Oral ethinyl estradiol and drospirenone
5. All of the above
Micronized progesterone is advised/approved for the following indications:

1. Primary endometrial protection in menopausal women on estrogen
2. Primary endometrial protection in women using vaginal estrogen
3. Primary treatment for sleep disorders in menopause
4. Primary treatment for irregular bleeding in menopause

All of the following are absolute contraindications to HT except:

- Acute liver disease
- Active thromboembolic disease
- Smoking
- Breast cancer

Transdermal estrogens do all the following except:

1. Improve HDL cholesterol
2. Increase the markers of inflammation such as C reactive protein
3. Decrease triglycerides
4. Have a demonstrable lower VTE risk compared to oral estrogens

Which technique should NOT be used to reduce the dose of transdermal estrogen?

1. Reduce the surface area of gel application
2. Reduce the number of pumps of gel
3. Cut the reservoir patch
4. Cut the matrix patch
5. Use a lower dose patch

Which of the following is INCORRECT regarding micronized progesterone?

1. Micronization prevents progesterone breakdown in the GI tract
2. Cannot be given to individuals with a peanut allergy
3. Is not metabolized by the liver
4. May exhibit somnolence as a side effect
5. Can be used in conjunction with estrogen patches

For women who have not had a hysterectomy, a progestin is recommended when using local (vaginal) estrogen.

1. True
2. False
The treatment of menopausal symptoms should not be started until a woman stops menstruating or has a documented FSH >26 micromoles/litre

1. True
2. False

Oral HT increases the risk of thrombotic events in:

a. Obese patients
b. In patients with a family history of DVT
c. In long-term users of HT
d. In new users of HT
e. In surgical patients

1. ALL OF THE ABOVE
2. NONE OF ABOVE
3. A AND C
4. B AND D
5. A,B,C AND D

The progestin addition to estrogen in HT:

1. Does not affect hot flash frequency
2. Does not affect incidence of breast cancer
3. Protects against endometrial cancer
4. Affects the incidence of DVT
5. Provides contraception

Current indications for HT in 2011 state that HT:

1. Can only be prescribed for 5 years
2. Is a good therapy for symptomatic patients with osteoporosis
3. Improves mood for perimenopausal patients
4. Improves memory in menopausal patients
5. Prevents myocardial infarctions

HT is associated with a reduction in mortality if initiated in women under 60 years old or within 10 years of menopause onset.

1. True
2. False

The risk of VTE increases with the duration of HT.

1. True
2. False
There is some good evidence confirming that black cohosh, red clover and/or evening primrose oil decrease the amount of hot flashes in menopausal women compared to placebo.

1. True
2. False

A 51-year-old woman has transdermal estradiol gel and an oral progestin for her menopausal symptoms. She is using 2 pumps (2.5 g) / day but tells you that she has not had much improvement. Your next most appropriate step is to:

1. Measure serum levels of estradiol
2. Review with her how and where she is applying gel
3. Increase to three pumps/day
4. Add a local vaginal estrogen
5. Add a low dose SNRI

A 45-year-old woman has had an early spontaneous menopause. She has chosen EPT to manage disruptive symptoms. She is particularly bothered by sleep disruption, which is compromising her day time function. Which of the following will you recommend?

1. Combination transdermal EP patch
2. Combination oral estradiol and norethindrone acetate
3. Transdermal estradiol gel and medroxyprogesterone acetate po
4. Estradiol patch and micronized progesterone
5. All of the above

<table>
<thead>
<tr>
<th>Conjugated estrogen</th>
<th>Person years</th>
<th>Multi-variate RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>313,661</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>0.3 mg</td>
<td>19,964</td>
<td>0.58</td>
<td>0.37-0.92</td>
</tr>
<tr>
<td>0.625 mg</td>
<td>116,150</td>
<td>0.54</td>
<td>0.44-0.67</td>
</tr>
<tr>
<td>1.25 mg</td>
<td>39,026</td>
<td>0.70</td>
<td>0.51-0.97</td>
</tr>
</tbody>
</table>

*MP is associated with a lower incidence of bleeding*
**Comparison of Bleeding Patterns With Cyclic Progestogens**

<table>
<thead>
<tr>
<th>12 d/mo x 12 mo</th>
<th>MPA, 10 mg/d (n=28)</th>
<th>Norpregestone acetate, 10 mg/d (n=22)</th>
<th>Hydrogesterone, 10 mg/d (n=20)</th>
<th>MP, 200 mg/d (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cycles evaluated</td>
<td>224</td>
<td>262</td>
<td>226</td>
<td>225</td>
</tr>
<tr>
<td>Duration of regular progestogen-related bleeding, median (range)</td>
<td>3.9 (2.8-5.1)</td>
<td>4.1 (3.1-5.3)</td>
<td>4.0 (2.6-5.6)</td>
<td>4.4 (2.9-5.9)</td>
</tr>
<tr>
<td>Irregular bleeding (% of cycles)</td>
<td>8.4%</td>
<td>5.7%</td>
<td>7.5%</td>
<td>12%*</td>
</tr>
<tr>
<td>Spotting (% of cycles)</td>
<td>9.8%</td>
<td>6.8%</td>
<td>8.8%</td>
<td>16%**</td>
</tr>
<tr>
<td>Amenorrhea (% of cycles)</td>
<td>9.8%</td>
<td>5.7%</td>
<td>8.4%</td>
<td>7.5%</td>
</tr>
</tbody>
</table>

*P<0.05 vs. nomogestrol acetate. **P<0.05 vs. nomogestrol acetate and dydrogesterone; P=0.051 vs. MPA.

**Postmenopausal HT and Risk of VTE: Results of the E3n Trial (cont’d)**

<table>
<thead>
<tr>
<th>Age/adjusted HR</th>
<th>Multivariate-adjusted HR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No progestogen use (n=26)</td>
<td></td>
</tr>
<tr>
<td>Current use of micronized progesterone (n=47)</td>
<td>0.9 (0.6-1.4)</td>
</tr>
<tr>
<td>Current use of norpregnane derivatives (n=69)</td>
<td>1.4 (0.8-2.5)</td>
</tr>
<tr>
<td>Current use of nortestosterone derivatives (n=22)</td>
<td>1.0 (0.7-1.5)</td>
</tr>
</tbody>
</table>

*Adjusted for age, body mass index, parity, educational level and time period.

**Progestogens**

- Any substance that has progestational activity
- Includes “natural” and “bioidentical” progesterone and synthetic progestins
- Progestins are synthetic progestogens with biologic activity to progesterone
- Oral progesterone is broken down in GI tract and therefore is inactive
- Progestins were developed which are broken down in the GI tract; derived from progesterone or testosterone (19-nortestosterone) precursors
- Once micronization was discovered, progesterone could be given orally

**Progestogen Selection**

Two different classes of progestogens are used in HT:

1. 17-hydroxyprogesterone (norpregnane) derivatives (including medroxyprogesterone acetate [MPA], megestrol, and progesterone)
2. 19-nortestosterone derivatives (norethindrone and norethindrone acetate)

**WHI Re-analysis: Effect of Estrogen Alone on Major Outcomes for Women <60 Years Old**

<table>
<thead>
<tr>
<th>Event</th>
<th>% difference in RR to Placebo (95% CI)</th>
<th># of events/10,000 women/yr of CEE alone therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>-37 (0.36-1.09)</td>
<td>-11</td>
</tr>
<tr>
<td>Stroke</td>
<td>-11 (-4.7-1.69)</td>
<td>-2</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>+37 (0.70-2.68)</td>
<td>+4</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>-18 (-0.65-1.04)</td>
<td>-8</td>
</tr>
<tr>
<td>Fractures</td>
<td>-30 (-0.59-0.83)</td>
<td>-56</td>
</tr>
<tr>
<td>New-onset diabetes</td>
<td>-12 (-0.77-1.01)</td>
<td>-14</td>
</tr>
<tr>
<td>Total mortality</td>
<td>-29 (-0.46-1.11)</td>
<td>-11</td>
</tr>
</tbody>
</table>

**WHI Re-analysis: Effect of Conjugated Equine Estrogen Alone on Stroke**

- Odds ratio 1.02 (95% CI 0.98-1.06)
- Number needed to treat 378 (95% CI 282-504)
- Number needed to harm 140 (95% CI 108-190)
- Total events 18 (95% CI 12-28)

[Link to the original WHI article](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2929333/)

[Link to the E3n Trial article](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1169733/)

[Link to Di Carlo et al. study](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1293281/)

[Link to de Ferrari et al. study](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2929333/)

[Link to the Menopause and Osteoporosis Update 2009](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2929333/)

[Link to the Canadian Consensus on Menopause, 2006 update](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2929333/)

[Link to the WHI Re-analysis](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2929333/)