BHRT in Females: Best Practice

Doreen Saltiel, MD JD FACC

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Evidence That Changed My Practice

- In PMP females, serum or validated dried-urine levels between the postmenopausal and luteal ranges can be used to monitor TD E2; however, a validated, peer-reviewed 4-spot dried urine test (DUTCH) is a better option
- TD Pg (non-vaginal) DOES NOT balance E2's endometrial proliferative effects
- In females, TD T doses as high as 10mg/d and pellet doses 50-150mg that increase serum TT levels above ULN (LC-MS/MS) are safe and do not result in adverse events
- Saliva SHOULD NOT be used to monitor HRT; there are no available validated assays with either clinical outcome data or serum equivalents
- Compounded creams may require higher doses than patches or gels to improve clinical outcomes

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Key Point

“Extrapolate when you can, rationalize when you must, but always individualize care.”

Doreen Saltiel, MD JD FACC

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Objectives

- **At the end of this presentation, attendees should have a better understanding of, and gain insights into:**
  - How the clinical evidence guides prescribing micronized progesterone (Pg), and which delivery methods and doses improve clinical outcomes
  - How the clinical evidence guides prescribing transdermal estradiol (TD E2), and which delivery methods and doses improve clinical outcomes
  - How the clinical evidence guides prescribing testosterone (T), and which delivery methods and doses improve clinical outcomes
  - Hormone-related guidelines' limitations

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Key Questions

- Why do we prescribe hormones?
- Why do we test hormones?
- What hormones should we prescribe?
  - What doses and delivery methods does the evidence support?
- What tests do we do?

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Why do We Prescribe Hormones?

Improve Clinical Outcomes

Pre/perimenopausal females

- Luteal phase defects
  - Adolescents
  - Reproductive women
- Perimenopause

Postmenopausal (PMP) females

- VMS
- VVA
- BMD
- Breast Cancer
- CVD Risk
- Maybe CNS benefits

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Why Do We Test Hormones?

- To make/exclude a diagnosis
- Monitor efficacy of therapy
- Ensure we are in the studied ranges that have proven to be safe and improve clinical outcomes

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Key Questions

- Why do w  rescribe hormones?
- Why do we te  ormones?
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  - What doses and delivery methods does the evidence support?
- What te  s do we do?

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Questions

- What is/are the treatment goals?
- What is the most effective dose to optimize the treatment goals?
- How best to limit all adverse events?

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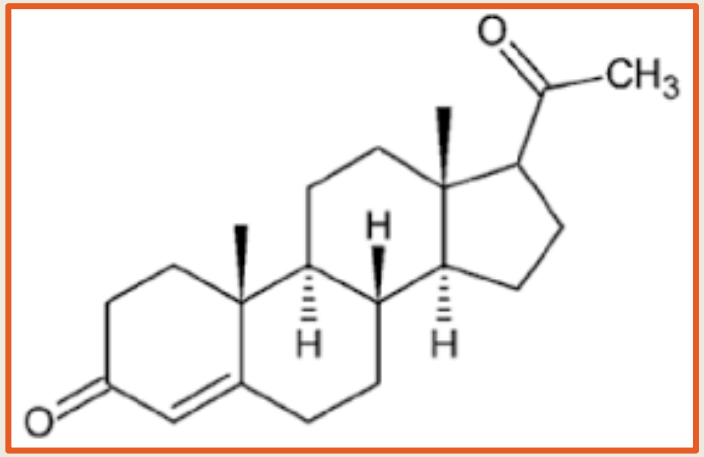
Progesterone (Pg)



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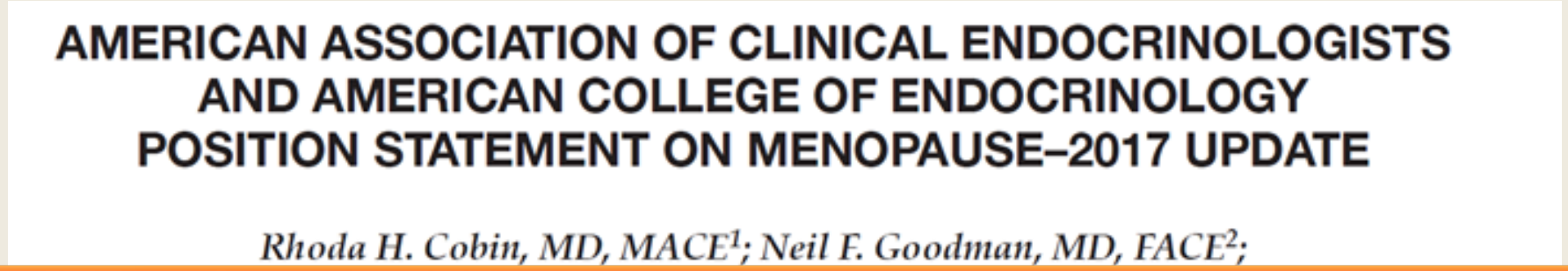
Progesterone Guidelines



AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
AND AMERICAN COLLEGE OF ENDOCRINOLOGY
POSITION STATEMENT ON MENOPAUSE–2017 UPDATE

Rhoda H. Cobin, MD, MACE[1]; Neil F. Goodman, MD, FACE[2];

- **When progesterone is necessary, [oral] micronized progesterone is considered a safer alternative.**
- **Oral micronized progesterone (OMP) 200mg protects the endometrium.**
- **Vaginal micronized progesterone (VMP) 100mg with a TD E2 0.025mg patch protects the endometrium.**

Cobin RH, Goodman NF. Endocr Pract. 2017; 23(7): 869-880

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Progesterone Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
AND AMERICAN COLLEGE OF ENDOCRINOLOGY
POSITION STATEMENT ON MENOPAUSE–2017 UPDATE

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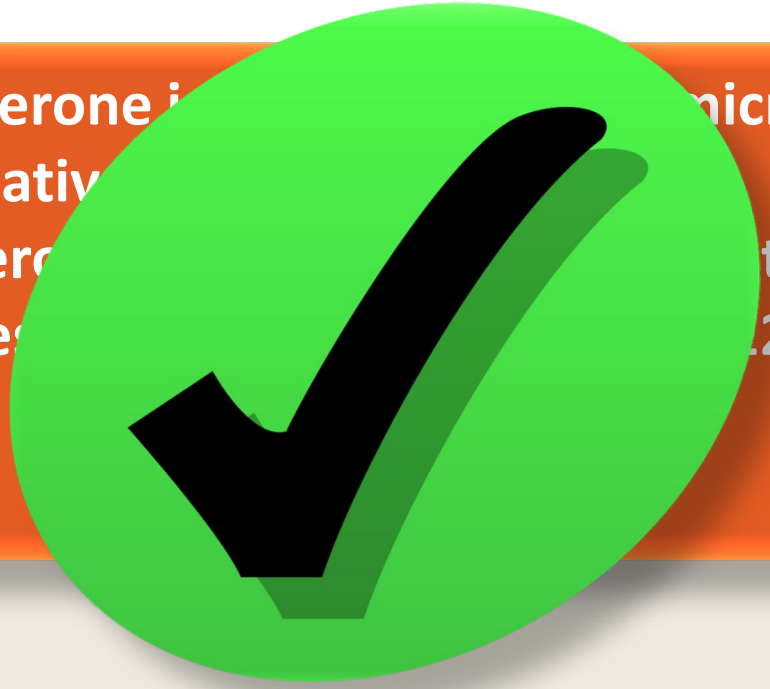
- Oral micronized progestero… the endometrium.
- Vaginal micronized proge… 2 0.025mg patch protects the endometrium.



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Micronized Progesterone's (Pg's) Benefits

Benefits

- Endometrial protection
- Optimizing BMD
- Vasomotor symptoms
- Sleep

Potential Benefits

- Neurobiological effects

Safety Issues

- Safe for the CV system
- Safe for the breast

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Endometrial Hyperplasia and Cancer Studies Summarized		
Studies	**Study Drugs/Doses**	**Results**
Endometrial Hyperplasia		

PEPI	• CEE 0.625mg/d alone
	• CEE 0.625mg/d + OMP 200mg/d x 12 d
	• CEE 0.625mg/d + MPA 10mg/d x 12 d
	• CEE 0.625mg/d + MPA 2.5mg/d continuous
		• No endometrial hyperplasia in any progestogen treatment group
		• Increased endometrial hyperplasia in CEE-alone group
		  ○ 20% after 1st year
		  ○ 62% after 3 years

Moyer	• OESTROGEL 1.5mg (21-25d/month) + UTROGESTAN 200mg x last 14 days/month • OESTOGEL 3.0mg (21-25d/month) + UTROGESTAN 300mg x last 14 days/month	• No endometrial hyperplasia in either group • Higher TD E2 + OMP doses more marked endometrial secretory changes and withdrawal bleeding than lower doses • For maximal endometrial protection > 11 days necessary
Gillet	• Females who wished a monthly cycle: OESTOGEL 3.0mg (days 1-25) + UTROGESTAN 300mg (days 16-25) • Females who did not wish a monthly cycle: OESTROGEL 1.5mg + UTROGESTAN 100mg x days 1-21 or days 1-25	• Higher OMP doses necessary to induce a secretory endometrium and withdrawal bleeding • OMP 100mg/d days 1-25 controls OESTROGEL 1.5mg/d proliferative effects, with frequent amenorrhea, and minimal spotting • Prescribing TD E2 + OMP days 1-25 increases compliance
DiCarlo	• Group A: DERMESTRIL-50 (0.05mg/d) + oral PROMETRIUM 100mg days 14-25 • Group B: DERMESTRIL-50 (0.05mg/d) + oral PROMETRIUM 200mg days 14-25 • Group C: DERMESTRIL-50 (0.05mg/d) + vaginal PROMETRIUM 100mg days 14-25 • Group D: DERMESTRIL-50 (0.05mg/d) + vaginal PROMETRIUM 200mg days 14-25	• All treatment regimens provided endometrial protection • Vaginal delivery system led to greater compliance • A higher OMP dose may be necessary to ensure amenorrhea
Endometrial Cancer		
KEEPS	• PREMARIN 0.45mg/d + PROMETRIUM 200mg/d x 12d • CLIMARA 0.05mg/d + PROMETRIUM 200mg/d x 12d • Placebo	• No endometrial hyperplasia in either group

REPLENISH	• A single combined o-E2/OMP capsule containing one of four doses or placebo
	• o-E2 100mg/d + 100mg/d OMP
	• o-E2 50mg/d + 100mg/d OMP
	• o-E2 50mg + 50mg/d OMP
	• o-E2 25mg + 50mg/d OMP
	• Placebo
		• All regimens provided endometrial protection
		• E2 1mg/d +100mg OMP capsule @ 1 year
		  ○ Endometrial hyperplasia in 1 female
		  ○ Endometrial proliferation in 2.9%
		• E2 0.50mg/d + 50mg OMP capsule @ 1 year
		  ○ Endometrial proliferation in 0.3%

Pg and Endometrial Studies

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Oral Micronized Progesterone (OMP) and the Endometrium

- **OMP 200mg protects the endometrium**
  - Moyer (OS, 1993): OMP 200mg, 12-14 sequential days protects the endometrium; Oestrogel 1.5mg/d
  - PEPI (RCT, 1996): Landmark study; OMP 200mg x 12 days + CEE 0.625mg/d
  - DiCarlo (OS, 2010): OMP 200mg x 12 days + 0.05mg/d patch
  - KEEPS (RCT, 2014): OMP 200mg x 12 days + 0.05mg/d patch

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Oral Micronized Progesterone (OMP) and the Endometrium

- **OMP 100mg protects the endometrium**
  - Gillet (OS, 1994): OMP 100mg continuous + Oestrogel 1.5mg/d
  - DiCarlo (OS, 2010): 100mg x 12 days + 0.05mg patch/d
  - Mirkin (RCT, 2020): REPLENISH: OMP 100mg + 1mg oral E2 in a combination capsule
    - Found SS correlation between baseline E2 levels and baseline endometrial histology
      - Females with baseline E2 ≥ 10pg/mL were more likely to have at baseline a proliferative endometrium than females with a baseline E2 < 5pg/mL or in the 5 to < 10pg/mL range

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Oral Micronized Progesterone (OMP) and the Endometrium

- OMP 100mg protects the endometrium
  - Gillet (OS, 1994): OMP 100mg continuous + Oestrogel 1.5mg/d

Clinical Pearl: A woman's endometrial health pre-hormone initiation is key when determining initial OMP and TD E2 doses.

endometrium than females with a baseline E2 < 5pg/mL or in the 5 to < 10pg/mL range

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Vaginal Micronized Progesterone (VMP) and the Endometrium

- **VMP 100mg and 200mg protect the endometrium**
  - Ross (RCT, 1997): VMP 90mg QOD, days 17-27 + CEE 0.625mg/d
    - Achieved luteal serum Pg level: 6.8ng/mL (mean)
  - DiCarlo (OS, 2010): VMP 100mg or 200mg x 12 days + TD E2 patch 0.05mg/d
- **VMP 45mg protects the endometrium**
  - Ross (RCT, 1997): VMP 45mg QOD, days 17-27 + CEE 0.625mg/d; 1/15 with endometrial proliferation, no hyperplasia, mean serum Pg level: 4.6ng/mL
  - De Ziegler (OS, 2000): VMP 45mg, either sequentially or continuously + either CEE 0.625mg/d, oral E2 2mg/d, or TD E2 patch 0.05mg/d
  - Hodis (RCT, 2016): ELITE: VMP 45mg days 1-10 + oral E2 1mg/d

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TD Pg and the Endometrium

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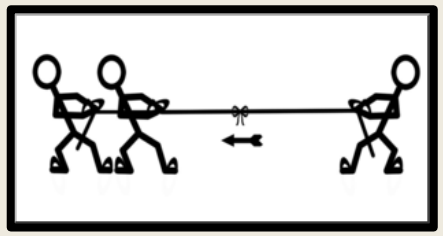
TD Pg: Not Recommended for Endometrial Protection

TD Pg is NOT Protective

- **Wren (2000) 3-month pilot study**
  - Determine TD Pg's endometrial effects
  - TD E2 0.1mg/d patch w/ either: TD Pg 16, 32, or 64mg x 14 days
  - No endometrial protection, No progestogenic effect
  - Saliva levels way exceeded serum luteal levels, with no endometrial effect
- **Vashisht (2005) 4-year open study**
  - TD Pg's endometrial effects
  - Oestrogel 1mg/d + TD Pg 40mg/d continuously
  - 32% endometrial proliferation or hyperplasia

TD Pg is Protective

- **Leonetti (2005) 1-year RCT**
  - Determine TD Pg's endometrial effects
  - TD Pg 20mg BID added to CEE 0.625mg/d protects the endometrium
  - Results are encouraging
  - "Although the lack of endometrial hyperplasia is promising, additional longer clinical trials to ensure safety are required before transdermal PC can be offered as an alternative to standard HRT."



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TD Pg: Not Recommended for Endometrial Protection

TD Pg is NOT Protective

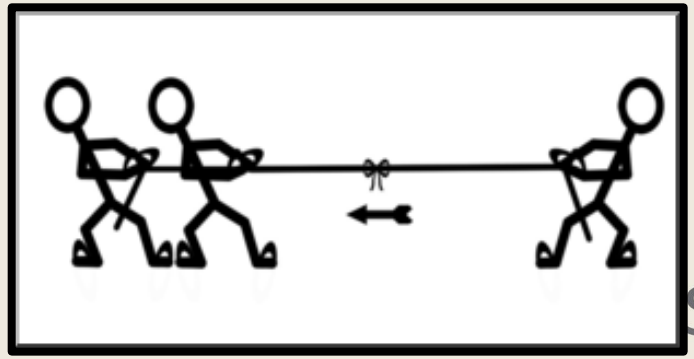
- **Wren (2000) 3-month pilot study**
  - with no endometrial effect
- **Vashisht (2005) 4-year open study**
  - TD Pg's endometrial effects
  - Oestrogel 1mg/d + TD Pg 40mg/d continuously
  - 32% endometrial proliferation or hyperplasia

TD Pg is Protective

- **Leonetti (2005) 1-year RCT**

Clinical Pearl: Though it may improve VMS, don't use TD Pg to protect the endometrium. In addition, it does not improve BMD.

clinical trials to ensure safety are required before transdermal PC can be offered as an alternative to standard HRT."



Wren B. Med J Aust. 2005; 182(5): 237-239.

Key Points: Pg and the Endometrium

- A female's pre-treatment endometrial health is important when considering both TD E2 and micronized progesterone dosing
- OMP 200mg is guideline recommended and is a reasonable first choice for endometrial protection; OMP 100mg also protects the endometrium
- VMP 100mg daily initially, is a reasonable alternative to OMP 200mg for endometrial protection; VMP 45mg daily also protects the endometrium
- Don't use TD Pg to protect the endometrium, the evidence doesn't support its use
- No lab test tells us about Pg's effect on the endometrium, so follow the clinical data

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Micronized Progesterone's (Pg's) Benefits

Benefits

- Endometrial protection
- **Optimizing BMD**
- Vasomotor symptoms
- Sleep

Potential Benefits

- Neurobiological effects

Safety Issues

- Safe for the CV system
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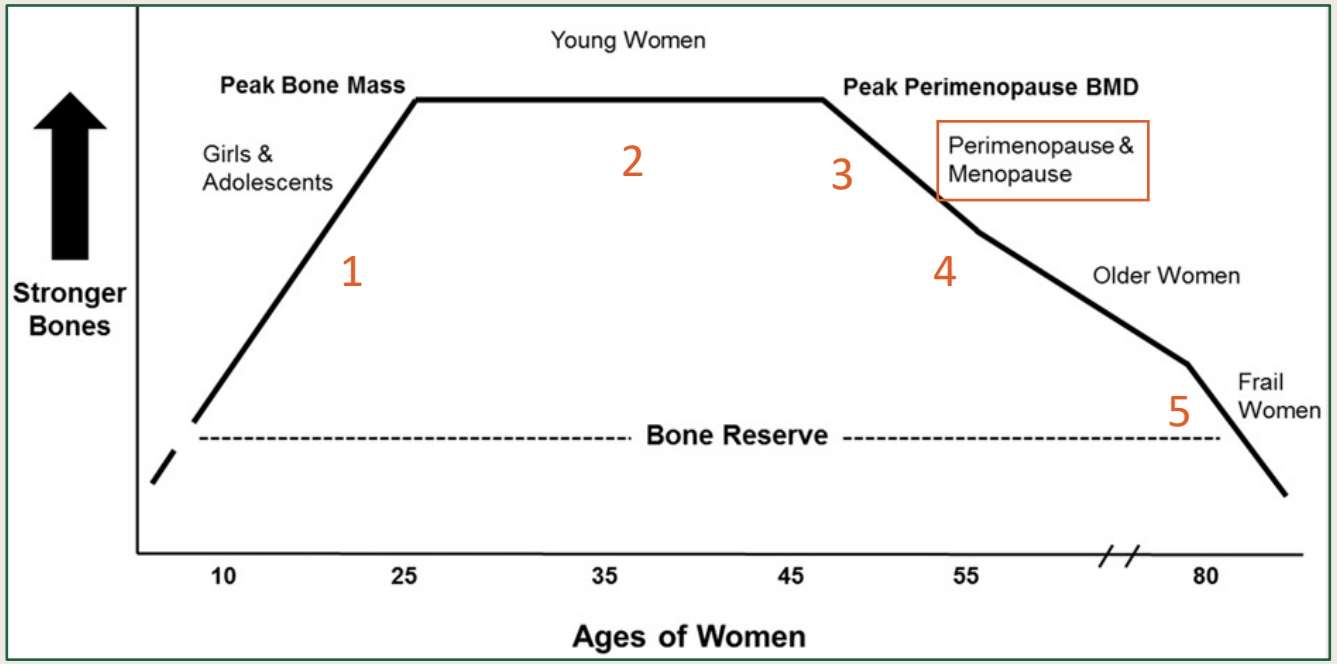
Pg and Bone Mineral Density (BMD)

- **Pg, in addition to E2, is necessary for optimal BMD**
  - E2 prevents bone resorption and Pg makes new bone
  - During a normal cycle, E2 and Pg are balanced, and BMD is stable
  - The ovulatory cycle needs to be 12-16 days (LH surge) for optimal Pg bone formation
- **At risk young females: have a high index if suspicion!**
  - Adolescents, premenopausal females, and perimenopausal females commonly have clinically normal cycles with ovulatory disturbances: short luteal phases with low Pg or anovulation
  - HPA axis dysfunction thought to be a root cause
    - Increases bone resorption by inhibiting calcium absorption and gonadal steroid production and release
    - Prevents new bone formation by inhibiting Pg and T's osteoblast effects

Pg and Bone Mineral Density (BMD)



- **Theoretical ideal lumbar spine (L1-4) areal BMD lifecycle:**
  - 1. Increase in BMD during childhood and adolescence
  - 2. Balanced BMD during the premenopausal years
  - 3. Perimenopause with skipped cycles results in bone resorption > bone formation = bone loss
  - 4. Menopause with ∅ cycles results in rapid bone loss, that becomes more gradual with time
  - 5. With frailty, rapid bone loss occurs again, with increased risk of fragility fractures

Adapted from: Prior JC. Climacteric. 2018; 21(4): 366-374.

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Pg, BMD, and Treatment

- **Adolescent and reproductive age females**
  - Address the HPA axis, the gut, etc.
  - OMP 300mg days 14-27 with oligomenorrhea and 14 days on and 14 days off with amenorrhea
- **Perimenopausal and PMP females**
  - There are no outcome studies evaluating progesterone alone regarding BMD and fracture risk in perimenopausal and PMP females
  - Prior et al., in 2017 published a RCT meta-analysis that included more than 1000 females; PMP females (~ 52 years old) were randomized to either E alone (mostly CEE 0.625mg/d), or CEE + mainly a progestin medroxyprogesterone (MPA) 2.5mg/d
    - Combined therapy SS improved BMD to a greater degree than E alone
    - OMP 200mg thought to provide same BMD protection as MPA 2.5mg (no data)

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Pg and Bone Mineral Density (BMD): Treatment

- **Adolescent and reproductive age females**
  - Address the HPA axis and all other underlying potential etiologies

Clinical Pearls: [1] Pg is E2's physiologic partner.
[2] In premenopausal females with LPDs, OMP 300mg is recommended.
[3] In PMP females, OMP 200mg is a reasonable starting doses for both endometrial protection and BMD.

0.0025mg/d), or CEE + mainly a progestin medroxyprogesterone 2.5mg/d

- Combined therapy SS improved BMD to a greater degree than E alone

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How do we translate this into clinical practice?

capecodhealth.org

retprogram.org

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Serum: The Gold-Standard for Hormone Testing

Before choosing a test other than the gold-standard, has the test been validated against the gold-standard, or studied and documented to improve clinical outcomes!

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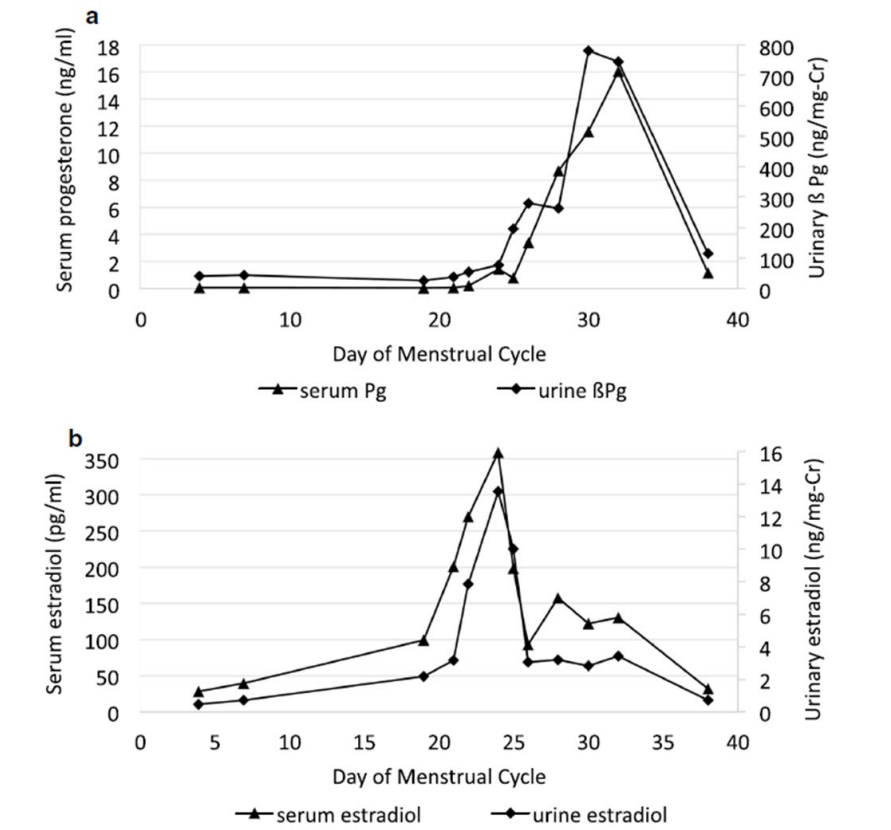
A Validated Dried-Urine Test



Newman M, et al. BMC Chem. 2019; 13(1): 20.

METHODOLOGY ARTICLE Open Access

Evaluating urinary estrogen and progesterone metabolites using dried filter paper samples and gas chromatography with tandem mass spectrometry (GC–MS/MS)

Mark Newman[1*], Suzanne M. Pratt[2], Desmond A. Curran[1] and Frank Z. Stanczyk[3]

- Prospective observational study comparing premenopausal (cycle map) and PMP (single day) urine and serum samples
  - Dried urine vs serum
  - Dried urine vs liquid urine
- **Conclusion:**
  - **For E2 and Pg, the dried urine assay is a good surrogate for serum testing**
  - **The 4-spot dried urine results are comparable to liquid urine**

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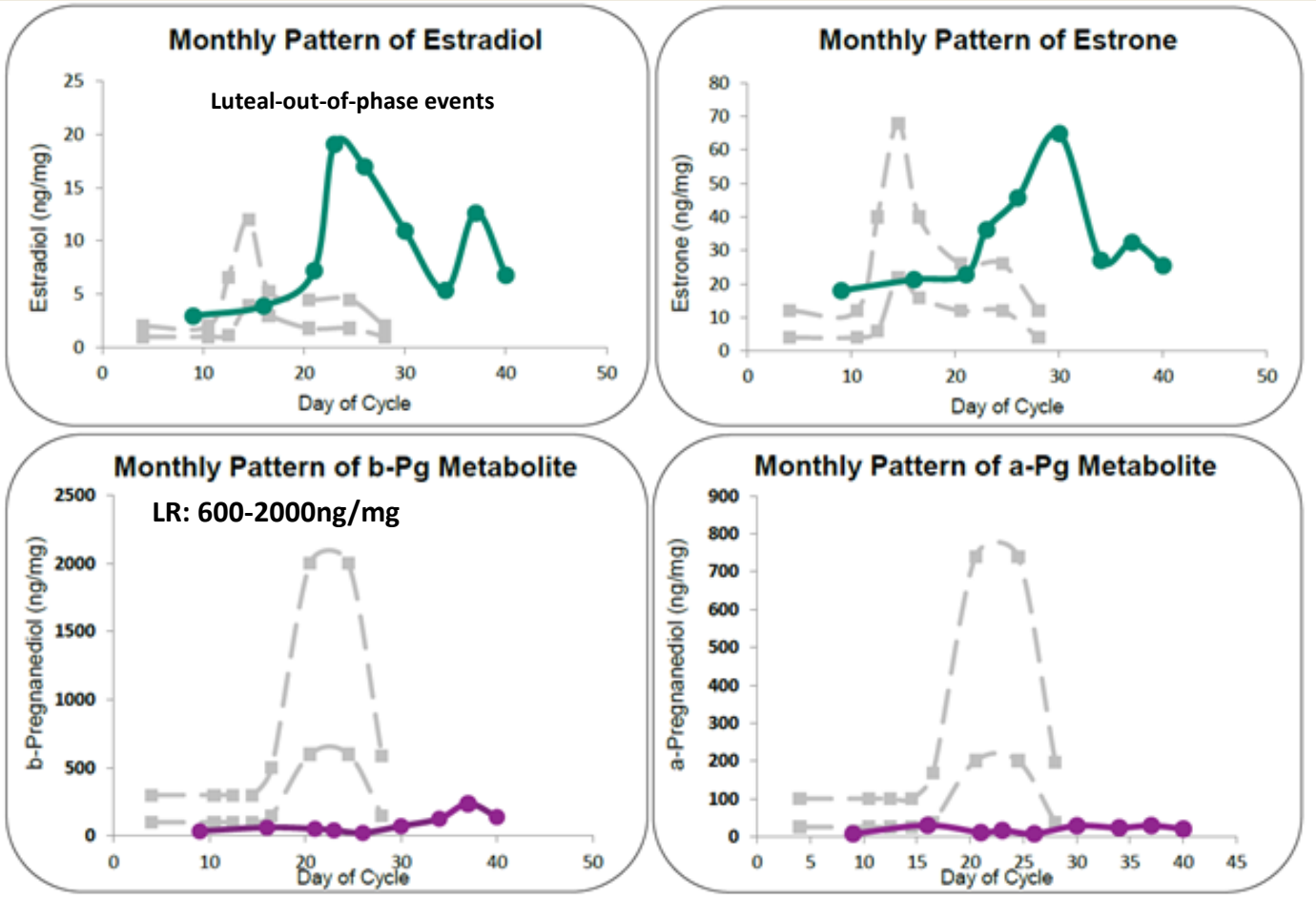
Urine Testing and LPDs: Have a High Index of Suspicion



Bone Mineral Density

- For optimal BMD luteal phase needs to be 12-16 days
- Short cycles (< 12-16 days by LH peak) or anovulation increase risk of bone loss
- 1-year study in premenopausal females documented:
  - **BMD maintained: normal ovulatory cycles or only 1 short cycle**
  - **Bone loss: more that 1 short cycle, or any anovulatory cycles**

- ****A Normal menstrual cycle does not necessarily = an ovulatory cycle**

Prior J, et al. N Engl J Med. 1990; 323(18): 1221-1227.
Prior J. Climacteric. 2018; 21(4): 358-365.

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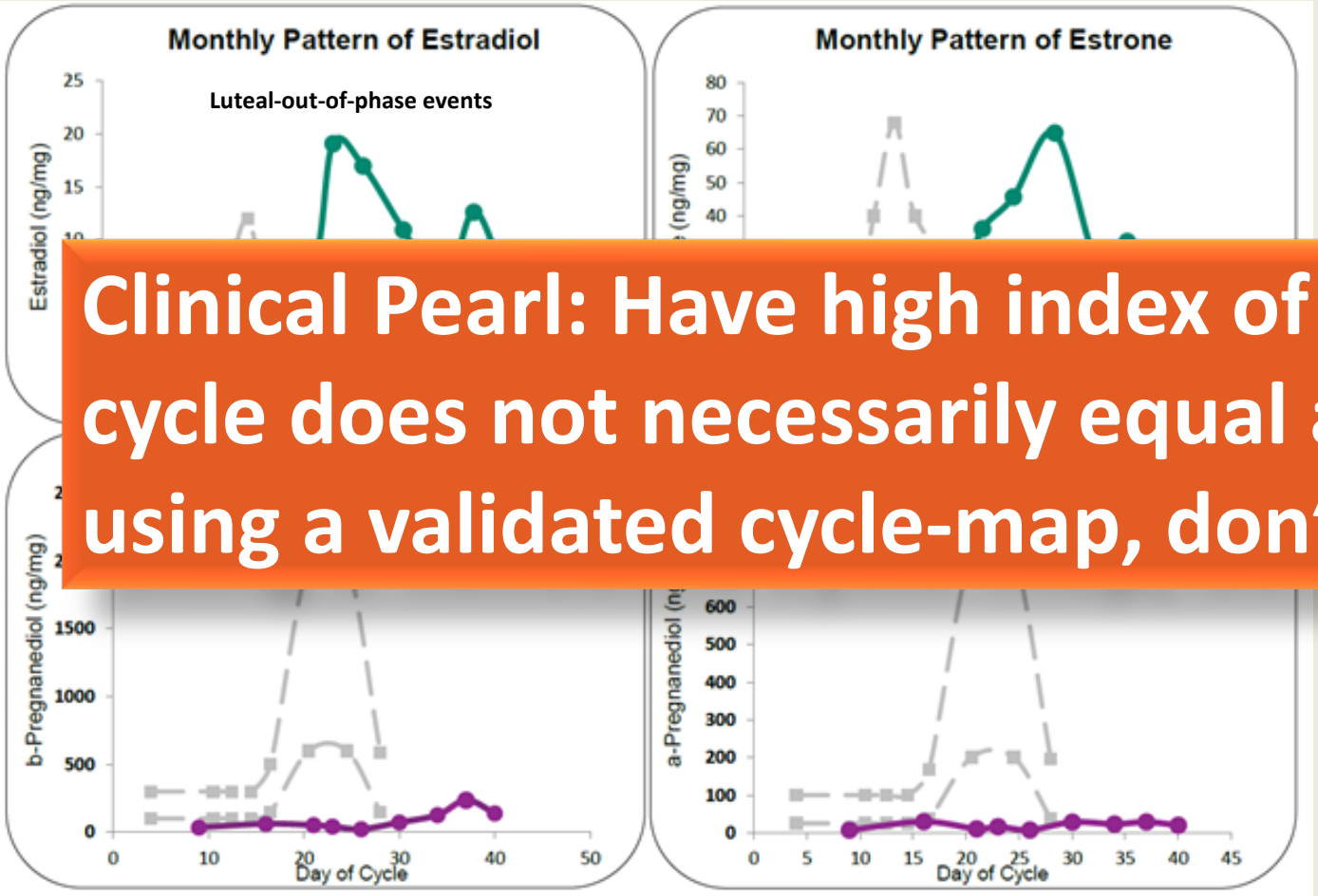
Urine Testing and LPDs: Have a High Index of Suspicion



Clinical Pearl: Have high index of suspicion, a normal cycle does not necessarily equal an ovulatory cycle; test, using a validated cycle-map, don't guess!

Bone Mineral Density

- For optimal BMD luteal phase needs to be 12-16 days
- Short cycles (< 12-16 days by LH peak) or anovulation

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- ****A Normal menstrual cycle does not necessarily = an ovulatory cycle**

Prior J, et al. N Engl J Med. 1990; 323(18): 1221-1227.
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Key Points: Pg BMD

- Pg is important for optimal BMD
- Normal length luteal cycles (12-16 days) are necessary for optimal BMD
- Test, don't guess; a validated cycle-map test provides the most actionable information for cycling females
- In adolescents, pre and perimenopausal females OMP 300mg is a reasonable choice, VMP 100-300mg, checking serum levels to ensure in "luteal range" is also a reasonable choice
- In all PMP females, follow the clinical data: OMP 200mg is reasonable; VMP 100 or 45mg, should result in serum levels at the lower end of the luteal range

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Pg Practice Pointers

- In premenopausal females with LPDs, including PCOS patients: OMP 300mg days 14-25, or VMP 100-300mg days 14-25 is recommended
- In PMP females with a uterus: OMP 200 or 100mg and VMP 100mg or 45mg daily protects the endometrium and may prevent osteoporosis
  - It is unclear whether OMP 100mg provides the same BMD protection as OMP 200mg (no data)
  - If using VMP, check serum levels to ensure in the lower end of the luteal range for BMD (plausibility argument)
- In PMP females without a uterus: OMP 200mg or 100mg or VMP 100mg or 45mg daily are reasonable starting doses; however, remember, Pg needs to balance TD E2 to avoid E dominance and approximate luteal levels to prevent osteoporosis

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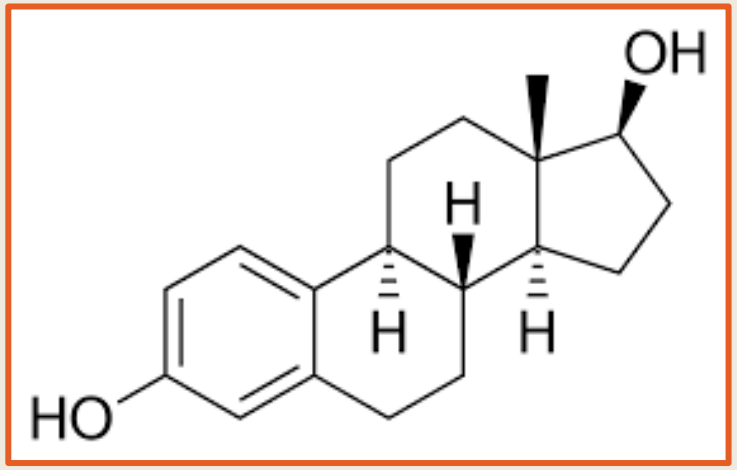
Estradiol (E2)



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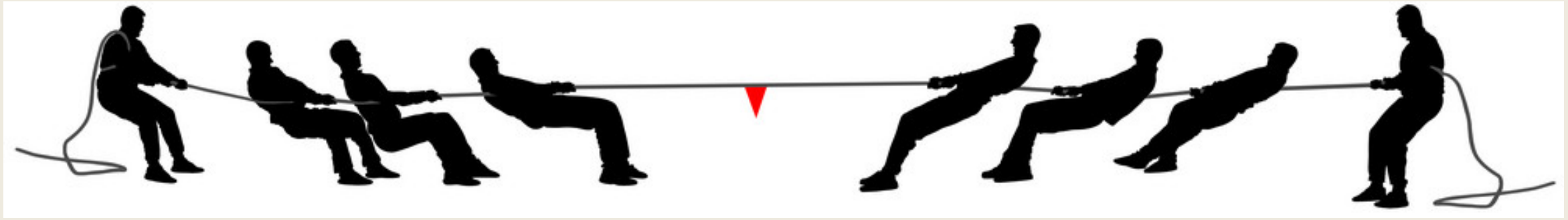
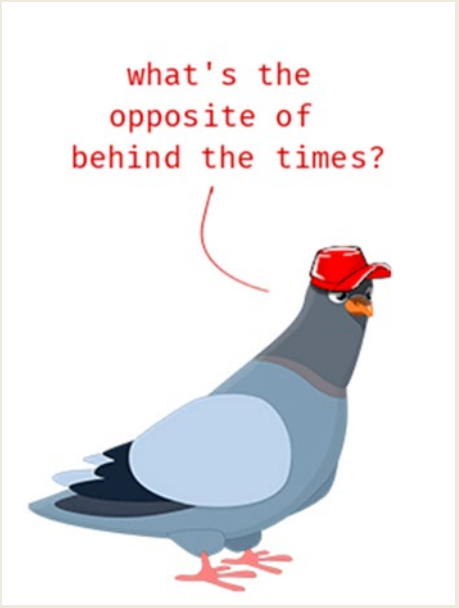
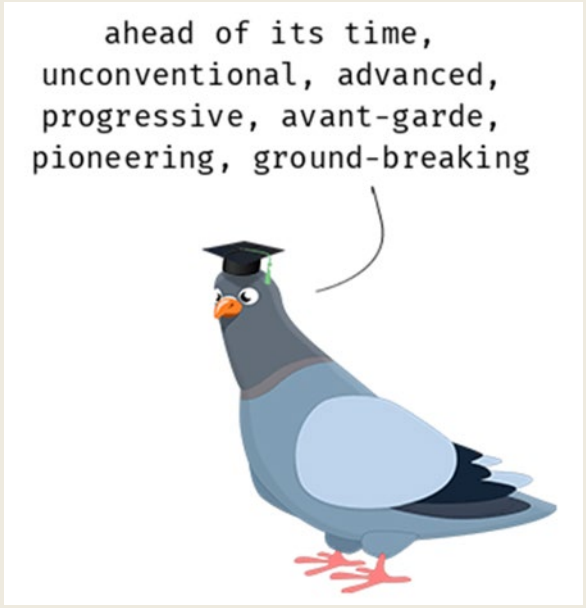
Allopathic Medicine vs Function Medicine







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MHT Guidelines

Menopause: The Journal of The North American Menopause Society
Vol. 29, No. 7, pp. 767-794
DOI: 10.1097/GME.0000000000002028

NAMS Position Statement

The 2022 hormone therapy position statement of The North American Menopause Society

- **"[M]HT remains the most effective treatment for VMS and the GSM and has been shown to prevent bone loss and fracture. Risks differ depending on the type, dose, duration of use, route of administration, timing ….**
- **Treatment should be individualized …, using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation of the benefits and risks of continuing or discontinuing [M]HT.**
- **For women aged younger than 60 years or who are within 10 years of menopause and have no contraindications, the benefit-risk ratio is most favorable for treatment of bothersome VMS and for those at elevated risk for bone loss or fracture."**

Pinkerton JV, et al. Menopause. 2017; 24(7): 728-753.
Pinkerton JV. Clin Obstet Gynecol. 2018; 61(3): 447-453.
Faubion SS, et al. Menopause. 2022; 29(7): 767-794.

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- **"For women who initiate [M]HT more than 10 or 20 years from menopause onset or are aged 60 years or older, the benefit-risk ratio appears less favorable because of the greater absolute risk of coronary artery disease, stroke, venous thromboembolism, and dementia."**

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Menopause: The Journal of The North American Menopause Society
Vol. 29, No. 7, pp. 767-794
DOI: 10.1097/GME.0000000000002028

NAMS Position Statement

The 2022 hormone therapy position statement of The North American

- **"For women who initiate [M]HT more than 10 or 20 years from menopause onset or are aged 60 years or older, the benefit-risk ratio appears less favorable because of the greater absolute risk of coronary artery disease, stroke, venous thromboembolism, and dementia."**

- **The statement above is based on the WHI data, which are no longer relevant! In fact, guidelines remind us that OMP/VMP is the TOC, and TD E2 may be preferred, especially in certain high-risk populations.**
- **Prior to initiating MHT in all females, especially in older females, risk stratification (endometrial, breast, bone, CVD, and cognition) is a must, as is ongoing surveillance. Individualize care!**

Pinkerton JV, et al. Menopause. 2017; 24(7): 728-753.
Pinkerton JV. Clin Obstet Gynecol. 2018; 61(3): 447-453.
Faubion SS, et al. Menopause. 2022; 29(7): 767-794.

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Menopausal Hormone E2 Therapy

E2 Benefits

- Vasomotor Symptoms (VMS)
- Vulvovaginal Atrophy (VVA)
- Bone Mineral Density (BMD)
- Breast Cancer (BC)
- CVD

Potential Benefits

- Cognition

How do we optimize these?

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Key Points: Estradiol Improves VMS, VVA, BMD

- For most females, estradiol improves VMS, VVA, and BMD at serum LC-MS/MS or validated dried-urine levels just outside the PMP range (serum LC-MS/MS = 20-40pg/mL or dried-urine = 0.7-1.8ng/mg)
  - TD E2 patches improve: VMS, VVA, sexual function, BMD, and CVD; cognition data is mixed
  - Gels not approved for BMD
    - EstroGel 0.75mg/d at serum levels 33.5pg/mL improved BMD at 1-year
    - EstroGel 1.5mg/d at serum levels ~ 65pg/mL improved BMD at 6-months
  - Compounded creams may require a higher dose to achieve serum/urine levels documented to improve clinical outcomes

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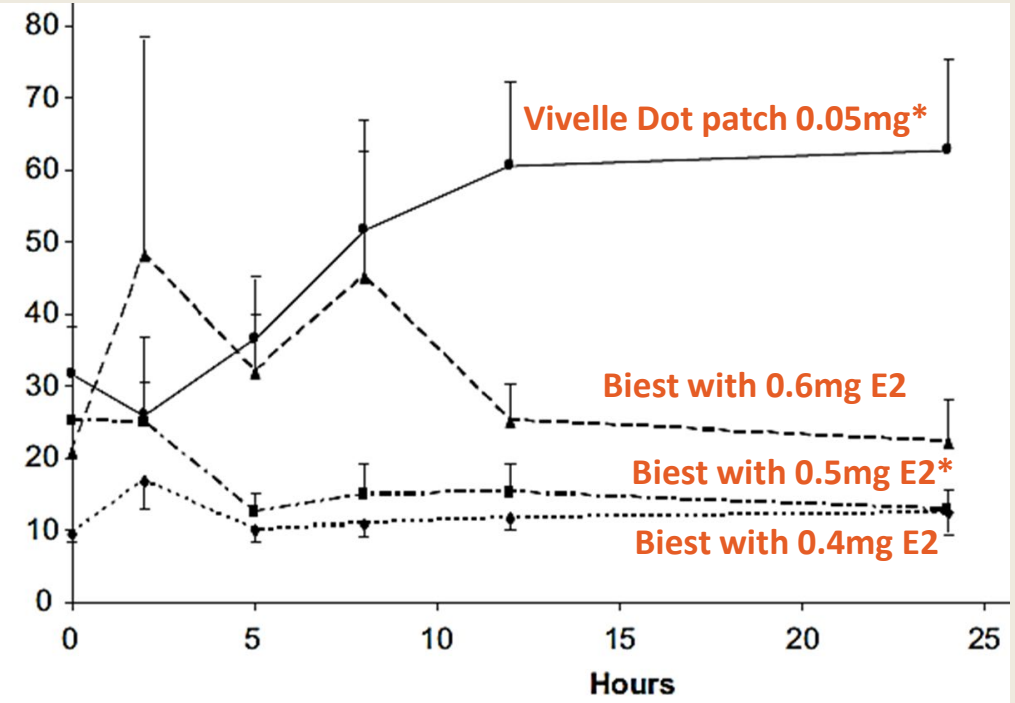
Patch vs Compounded Creams

Steady state serum LC-MS/MS levels



- Objective: Compare the pharmacokinetics compounded E2 creams vs TD E2 patch
- Study:
  - RCT study, 37 females, mean age 52, BMI ~ 24.5
  - First study to compare compounded E2 cream at different doses, with each other and an FDA-approved patch; E2 measured using LC-MS/MS
- Study drugs:
  - Biest 80: 20 with:
    - E2: 0.6mg, 0.5mg, and 0.4mg
  - Vivelle dot patch 0.05mg
  - Progesterone
    - Prometrium vs compounded OMP: equivalent
- **Conclusions:**
  - **Commonly used Biest doses yielded SS lower serum E2 levels than did the standard-dose patch**
  - **Biest serum levels had wide variations**
  - **More studies necessary to find comparable doses**

Sood R, et al. Maturitas. 2013; 74(4): 375-382.

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Menopausal Hormone E2 Therapy

E2 Benefits

- Vasomotor Symptoms (VMS)
- Vulvovaginal Atrophy (VVA)
- Bone Mineral Density (BMD)
- **Breast Cancer (BC)**
- CVD

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E2 Therapy: Breast Cancer (BC)

Both estrogen-alone and estradiol-alone decrease BC incidence and BC mortality

Mikkola TS, et al. Menopause. 2016; 23(11): 1199-1203.
Hodis HN, et al. Climacteric. 2018; 21(6): 521-528.
Chlebowski RT, et al. JAMA. 2020; 324(4): 369-380.

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Breast Cancer (BC) Studies Summarized		
WHI: CEE alone	• CEE 0.625mg/d alone vs placebo • Treatment for 7.2 years • 18 follow-up years	• Typical PMP female, no previous MHT • Decreased BC incidence, 45% BC mortality reduction
WHI: CEE + MPA	• CEE 0.625mg/d + MPA 2.5mg/d vs placebo • Treatment for 5.6 years • 18 follow-up years	• Typical PMP females, no previous MHT ○ Neutral effect on BC incidence and BC mortality • Older PMP females, who had previously used MHT prior to randomization, those randomized to the placebo arm had a lower BC incidence that all other WHI RCT placebo groups and the WHI-OS comparator group

WHI 2020 update	• CEE-alone vs placebo, 7.2 treatment years
	• CEE + MPA vs placebo, 5.6 treatment years
	• 20 follow-up years
		• CEE-alone vs placebo: decreased BC incidence and mortality
		• CEE + MPA: null effect on BC mortality (similar to placebo), but because of faulty analysis that was never corrected, still reporting increased BC incidence (See Hodis and Sarrel WHI 2018 reanalysis
		  ○ Placebo arm had a lower BC incidence than all other placebo groups in WHI studies
		  ○ CEE + MPA: no SS difference when compared to placebo

WHI: WHI-OS	• CEE 0.625mg/d (18.5 years treated) • CEE < 0.625mg/d (17.4 years treated) • TD E2 dose and delivery unknown (14 years treated) • 8.2-year follow-up study	• PMP females s/p hysterectomy • CEE 0.625mg/d vs CEE < 0.625mg/d: no difference in invasive BC risk • CEE 0.625mg/d vs TD E2: TD E2 with a non-significant decreased BC risk • Time since menopause had no effect on invasive BC risk
FINNISH -OS	• O-E2 1 or 2mg/d • TD E2 0.025-0.1mg/d patches • TD E2 0.5-1.5mg/d gels • Progestins used in PMP females with a uterus • Placebo	• All MHT users (even when combined with a progestogen) had an up to 54% BC mortality reduction • E2 alone had the greatest mortality reduction, regardless of age • Females 50-59 years old had the greatest mortality reduction • With E2 BC mortality 1 in 20 females, whereas without E2 BC mortality 1 in 10 women
Million Women's	• CEE, o-E2, TD E2, pellets: doses unknown • Never users (comparator)	• All increased BC "relative risk" and "relative" mortality risk • Increased BC and BC mortality occurred in females who likely had undiagnosed BC • Comparator group had a lower BC incidence than the general population, skewing the data
E3N	• Primarily TD E2 • Some used o-E2 • Never users (comparator)	• Increased BC "relative risk" • Data not clean: large percentage in the TD E2-only group used combined therapy and large percentage in the TD E2 + OMP group used a progestin

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WHI: Data Misinterpretation

- "…[A]ny association that may exist between HT and BC appears to be rare and no greater than any other medications commonly used in clinical medicine."[1]
- **E/E2 therapy decreases BC incidence and BC mortality**
  - The WHI study: only 10% females were 50-54 years old, was NOT a BC trial
  - CEE-alone vs placebo (WHI):
    - After 20 follow-up years, CEE-alone decreased both BC incidence and BC mortality (45% BC mortality reduction); median treatment 7.2 years
  - CEE + MPA vs placebo (WHI):
    - In the hormone naïve group vs placebo (75%): no difference in BC incidence
    - In the prior HRT treatment arm vs placebo (25%): falsely reported higher BC incidence, when the divergent curves were due to an unusually low placebo group BC incidence, not an increased BC incidence in the treatment arm; null effect on BC incidence; median treatment 5.6 years

[1] Hodis HN, et al. Climacteric. 2018; 21(6): 521-528.
Chlebowski RT, et al. JAMA. 2020; 324(4): 369-380.

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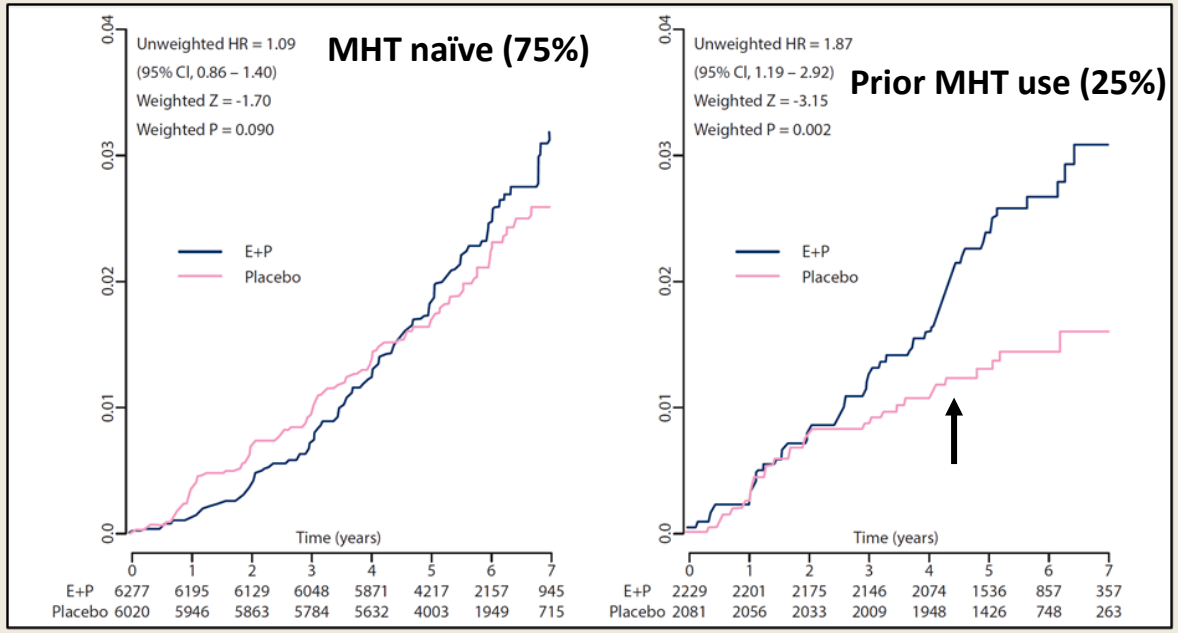
WHI: CEE + MPA

1



2

Subgroups	CEE + MPA Clinical Trial Placebo Group Annualized % Events	WHI-OS Hormone Therapy Non-Users Annualized % Events
No prior MHT use	0.36	0.35
Prior MHT use	0.25	0.38

3

Subgroup	CEE + MPA Clinical Trail CEE + MPA Group Annualized % Events	Dietary Modification Trial Low Fat Diet Group Annualized % Events	Dietary Modification Trial Usual Diet Group Annualized % Events
CEE + MPA overall	0.43	0.42	0.45

- **1. WHI + CEE vs Placebo Trial**
  - Average age 63.3 years, 12-years since menopause
  - Stratified by prior hormone use
  - Similar trends for all subgroups except prior MHT placebo arm
    - MHT prior use placebo arm: sharp divergence without explanation
  - This divergent trend line leads to false impression that treatment arm has higher BC incidence
  - Elevated HR due to DECREASED BC incidence in PLACEBO treated women
- **2. Comparison of BC incidence rates between WHI-RCT and WHI-OS CEE + MPA vs Placebo**
  - Marked difference in prior MHT placebo arm when compared to RCT no prior use placebo arm + WHI-OS equivalent
- **3. CEE + MPA RCT Treatment Arm Overall vs Dietary Modification (DM): BC was a primary outcome**
  - BC incidences = across all 3 groups

Hodis HN, et al. Climacteric. 2018; 21(6): 521-528.

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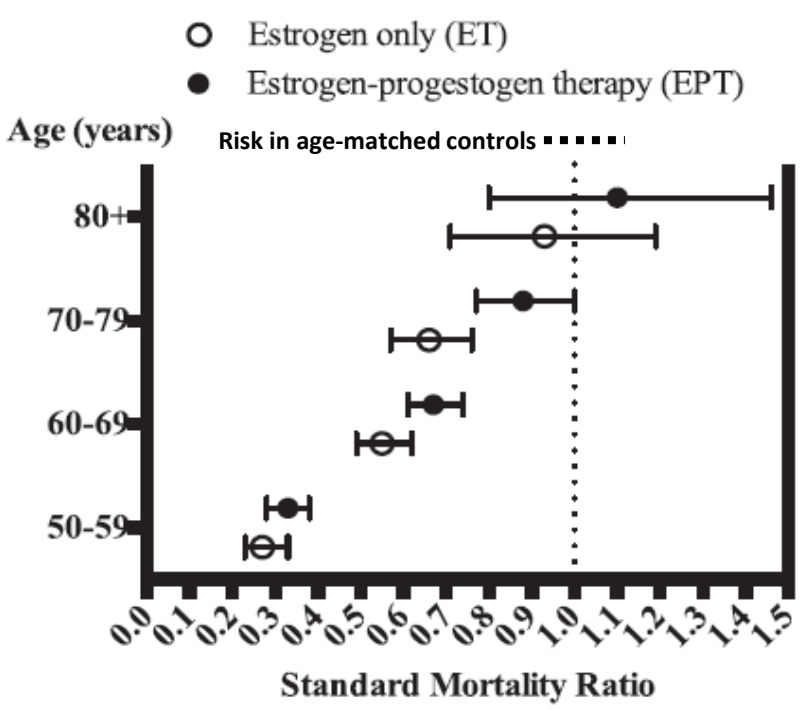
Estradiol Decreases BC Mortality

Reduced risk of breast cancer mortality in women using postmenopausal hormone therapy: a Finnish nationwide comparative study

Tomi S. Mikkola, MD, PhD,[1,2] Hanna Savolainen-Peltonen, MD, PhD,[1,2] Pauliina Tuomikoski, MD, PhD,[1] Fabian Hoti, PhD,[3] Pia Vattulainen, MSc,[3] Mika Gissler, M.SocSci, PhD,[4] and Olavi Ylikorkala, MD, PhD[1]



- Objective: To determine whether E2-alone or E2 combined with a progestin preceding a BC diagnosis would affect BC mortality
- Study: 15-year observational study using the Finnish Database
  - 489,105 PMP females mean age 52 years, mean MHT exposure: 6.8 ± 6.0 years
  - E2 formulations: o-E2 1-2mg/d, TD E2 patch 0.025mg-0.1mg/d or TD E2 gel 0.5mg-1.5mg/d
  - Progestins: norethisterone acetate (43%), MPA (30%), dydrogesterone (13%)
- Results: when compared to age-matched controls
  - E2-based HT was associated with an up to 54% BC mortality reduction
    - Females 50-59 had the greatest BC mortality reduction: 67%
    - Overall E2-alone: 44-51% SS mortality reduction, regardless of duration, and a greater mortality reduction than EPT use
    - Overall EPT: 32-50% SS mortality reduction, regardless of duration
  - Risk not related to MHT duration or age at onset

Mikkola TS, et al. Menopause. 2016; 23(11): 1199-1203.

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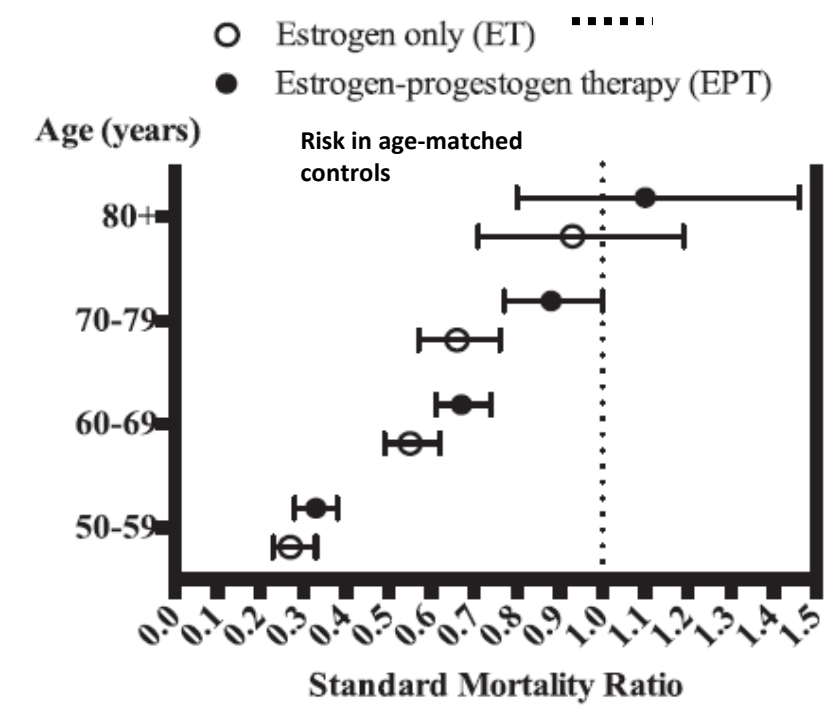

- **Conclusion: O-E2, TD E2 patches, and TD E2 gels SS decreased BC mortality up to 54%**
  - Largest mortality reduction was at 5-10 years, in females 50-59, and in those using E2-alone
  - Even when MHT use was > 10 years, BC mortality reduction
  - Age at initiation not related to BC mortality
  - **Whereas 1: 10 females die from BC in the general population, 1: 20 MHT users die from BC, a 50% mortality reduction**

Mikkola TS, et al. Menopause. 2016; 23(11): 1199-1203.

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- **Conclusion: O-E2, TD E2 patches, and TD E2 gels SS decreased BC mortality up to 54%**

Clinical Pearls: E2-alone decreases BC mortality, with the greatest mortality benefit in those 50-59-years old.
To maximize the E2-alone effects, VMP, may be a better option than OMP, though it has never been studied.

Mikkola TS, et al. Menopause. 2016; 23(11): 1199-1203.

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Key Points: Breast Cancer

- There is substantial evidence that TD E2-alone not only decreases BC incidence, but decreases BC mortality up to 54%
- Even females using combined MHT had a mortality benefit when compared to the age-matched population, however, E2-alone users had the greatest mortality benefit
- The greatest BC mortality benefit occurs in females 50-59 years old, however, age at hormone initiation and duration > 10 years is not associated with increased BC incidence or mortality
- Time since menopause and age > 60 should cause pause, not prevent MHT initiation or continuation

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E2 Benefits

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- Breast Cancer (BC)
- **CVD**

Potential Benefits

- Cognition

How do we optimize these?

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Estradiol Is Important For CV Health

- **E2, E3, Pg, and T are immune modulators and anti-inflammatory hormones**
  - E2's, Pg's, and T's anti-inflammatory actions include inhibiting proinflammatory cytokines: IL-6, IL-1β, and TNF-α and stimulating anti-inflammatory cytokines: IL-4, IL-10
  - E2 receptors (ERs), Pg receptors (PRs) and T receptors (TRs) are expressed in immune cells, endothelial cells, and vascular smooth muscle cells
  - Aging is associated with a decline in sex hormones, and both influence immune competence and disease susceptibility, i.e., CVD

Gubbels Bupp MR. Cellular Immunol. 2015; 294(2): 102-110.
Gubbels Bupp MR, et al. Front Immunol. 2018; 9: 1269.
Mauvais-Jarvis F, et al. Endocrinology. 2020; 161(9): bqaa127.

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Estradiol and the Endothelium

- **Estradiol's endothelial effects**
  - E2 increases endothelial NO production → vasodilation
  - E2 decreases endothelin-1, a potent vasoconstrictor and pro-inflammatory peptide secreted by the endothelium
  - E2 has direct antioxidant effects: scavenging/inhibiting ROS
  - E2 increases mitochondrial antioxidant defense
- **Estrogen receptor signaling: Use it or Lose it!**
  - The endothelium has both ER-α and ER-β receptors; ER-α >> ER-β
  - ER-α is a key determinant in maintaining endothelial vascular function
    - ER-α binding increases eNOS and SOD
  - E2 modulates endothelial cell ER expression, which impacts ER signaling, sensitivity, and function

Somani YB, et al. Am J Physiol Heart Circ Physiol. 2019; 317(2): H395-H404.

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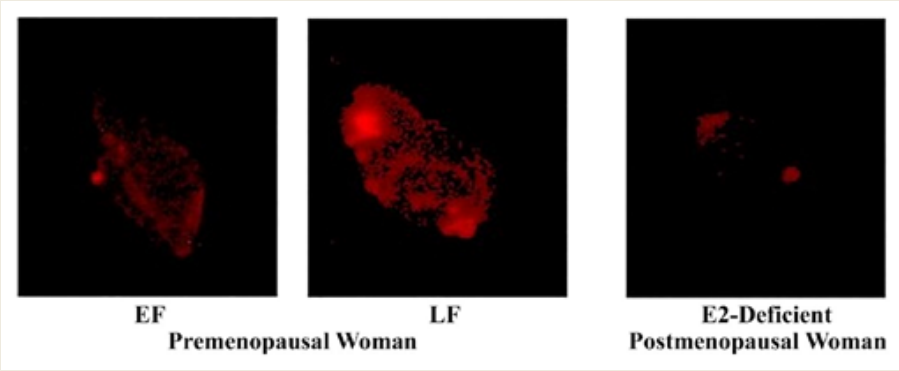
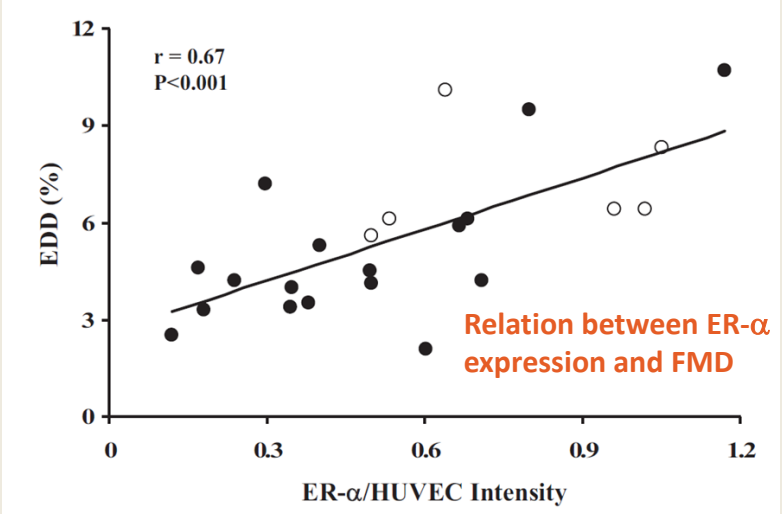
ER-α Endothelial Cell Expression: a Dynamic Process Dependent on E2 Status





- Objective: Determine whether vascular endothelial cell ER-α expression is influenced by E2 status and related to endothelial cell function
- Study: Observational study, 16 healthy premenopausal and 17 PMP females were studied
- Method: Immunofluorescent staining of peripheral venous endothelial cells and brachial artery flow-mediated vasodilation was performed
- Results:
  - Serum E2 levels
    - Premenopausal EF: 36 ± 7pg/mL; LF: 83 ± 17pg/mL
    - PMP: 30 ± 6pg/mL
  - ER-α expression
    - EF: 30% less than LF (SS, P < .0001)
    - PMP: 33% less than LF (SS, P < .0001)
  - ER-α expression positively associated with serum E2 levels, eNOS expression and activation
  - Endothelial-dependent vasodilation
    - 30% less in PMP females
    - Positively related to endothelial ER-α expression
    - Not related to CVD risk factors
- **Conclusion: Serum E2 may regulate ER-α expression, which influences endothelial function by modulating eNOS**

Gavin KM, et al. J Clin Endocrinol Metab. 2009; 94(9): 3513-3520.

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Question: Do the hormone changes that occur during the menopause transition accelerate vascular aging and contribute to endothelial dysfunction?

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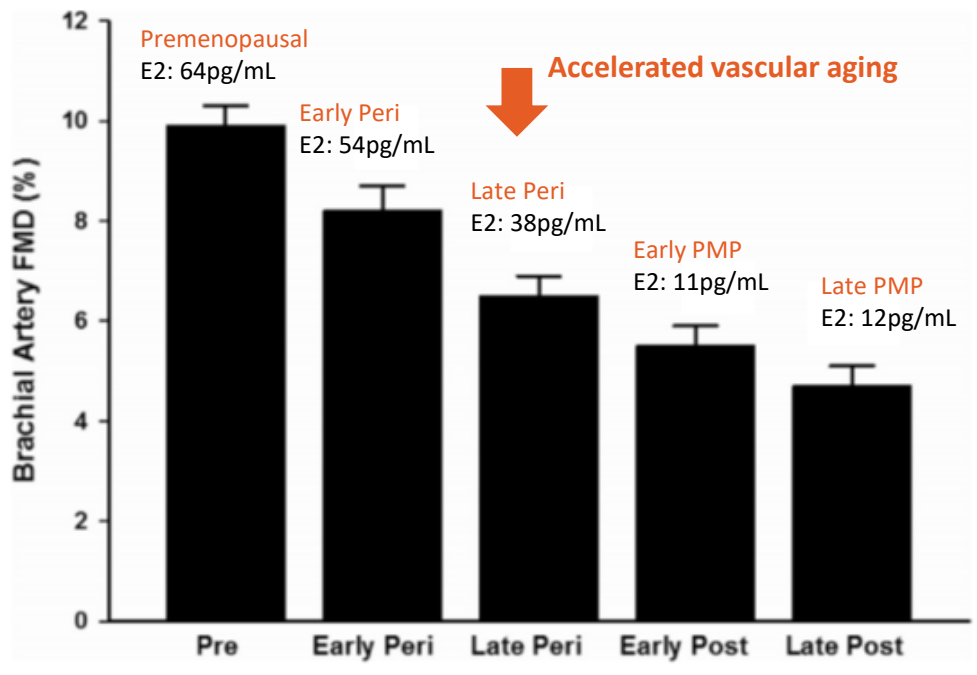
The Menopause Transition: an Overlooked Target

Endothelial Function Is Impaired across the Stages of the Menopause Transition in Healthy Women

Kerrie L. Moreau, Kerry L. Hildreth, Amie L. Meditz, Kevin D. Deane, and Wendy M. Kohrt



Early peri: 17% decrease vs Late peri: 34% decrease

- Objective: To determine whether the menopause transition affected endothelial function, as measured by brachial artery flow-mediated vasodilation (FMD)
- Study: Cross-sectional observational study involving 132 healthy females; not on hormone therapy/contraception for ≥ 6 months
  - Early peri: > 2 cycles, length ≥ 7d, **late peri: amenorrhea ≥ 2 months, but ≤ 12 months,** early PMP: ≤ 5 years, late PMP: > 5 years (STRAW criteria)
- Results:
  - **The menopause transition was associated with endothelial dysfunction, independent of traditional RF**
  - When compared to premenopausal females:
    - FMD was SS lower in early peri ($P = 0.03$) late peri ($P < 0.001$), and early and late PMP ($P < 0.001$)
  - Early peri hormone levels may be sufficient to provide some endothelial protection
  - **Late peri associated with a rapid decline in endothelial function that worsens with prolonged E2 deficiency**
    - SS lower FMD than either pre- or early peri females, but was NOT SS different than PMP females
  - PMP women, with prolonged E2 deficiency had the lowest FMD
  - Lower FMD strongly associated with higher FSH and lower E2 levels
- **Conclusion: Menopause is transition associated with a significant decline in endothelial function**

Moreau KL, et al. J Clin Endocrinol Metab. 2012; 97(12): 4692-4700.

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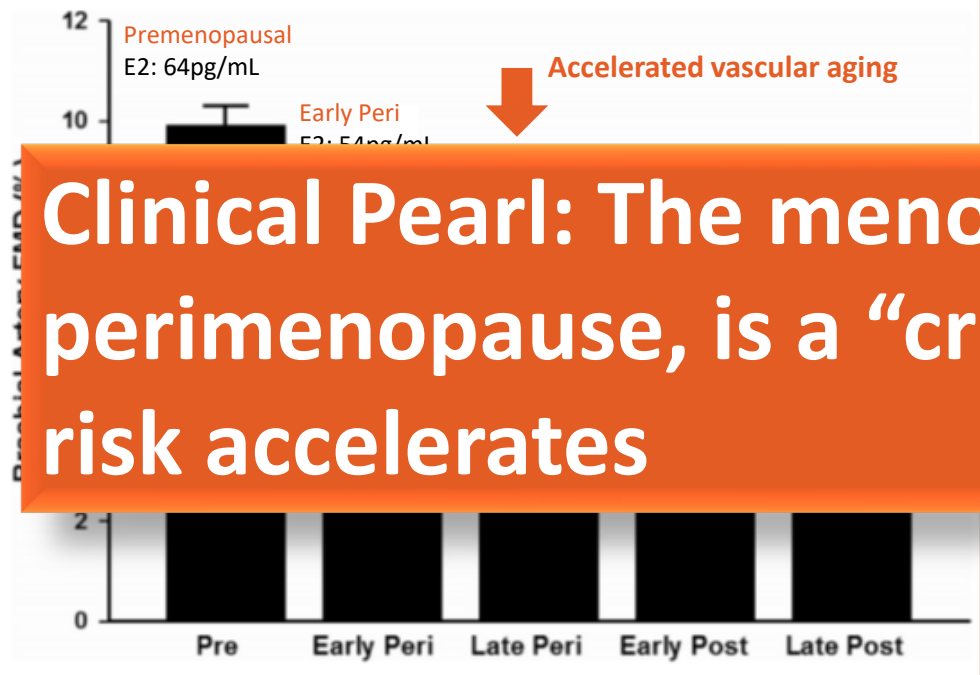

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- **Conclusion: Menopause transition is associated with a significant decline in endothelial function**

Clinical Pearl: The menopause transition, especially late perimenopause, is a "critical period" during which CVD risk accelerates

Early peri: 17% decrease vs Late peri: 34% decrease

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Question: Do the hormone changes that occur during the menopause transition accelerate vascular aging and contribute to endothelial dysfunction?

Yes!

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Question

In addition to traditional and other functional CV risk factors, what else do we need to ask about?

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Females, VMS, and CVD

Menopausal Vasomotor Symptoms and Risk of Incident Cardiovascular Disease Events in SWAN (Study of Women's Health Across the Nation)

Rebecca C. Thurston, PhD; Helen E. Aslanidou Vlachos, MSc; Carol A. Derby, PhD; Elizabeth A. Jackson, MD, MPH; Maria Mori Brooks, PhD; Karen A. Matthews, PhD; Sioban Harlow, PhD; Hadine Joffe, MD, MSc; Samar R. El Khoudary, PhD, MPH

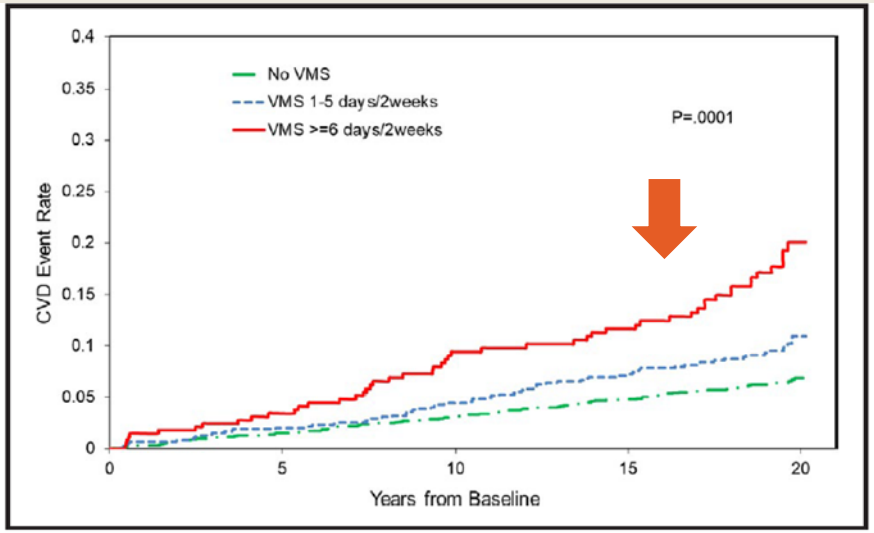

Figure 1. Baseline vasomotor symptoms (VMS) in relation to fatal and nonfatal cardiovascular disease (CVD) events, N=3083, 231 events.

- Objective: To determine whether frequent and/or persistent VMS were associated with the increased nonfatal and fatal CVD event risk
  - Whether females with [1] more frequent VMS at baseline or [2] persistently frequent VMS over time were at increased risk for subsequent CVD events
- Study: Longitudinal cohort study, midlife females followed for > 20 years
  - 3083 pre and early perimenopausal females, median age 46 years, followed up to 22 years
  - VMS categorized as:
    - None; 1-5 days/2 weeks (occasional); ≥ 6 days/2 weeks (frequent)
  - Median E2 levels using an immunoassay: 57.7pg/mL (no VMS); 52.1pg/mL (occasional); 48.3pg/mL (frequent)

- **Associations not explained by traditional RF or serum E2 levels**

Thurston RC, et al. J Am Heart Assoc. 2021; 10(3): e017416.

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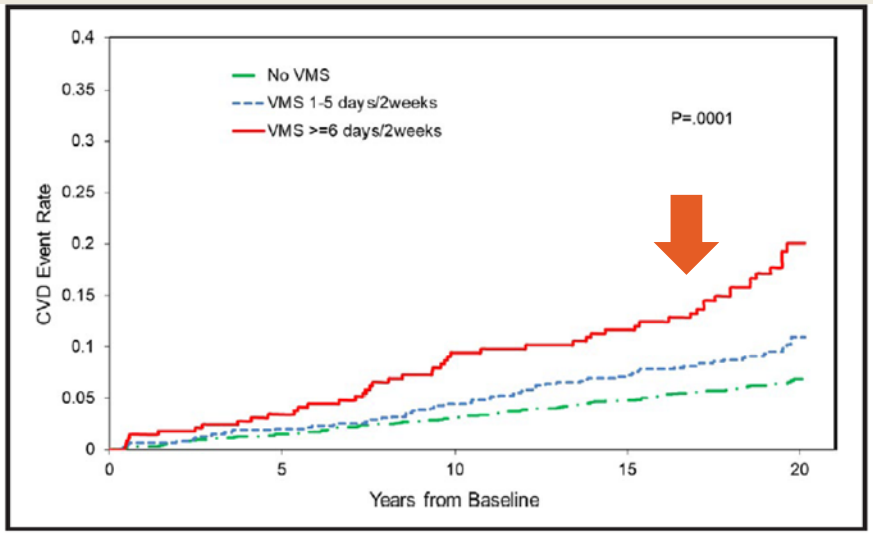

Figure 1. Baseline vasomotor symptoms (VMS) in relation to fatal and nonfatal cardiovascular disease (CVD) events, N=3083, 231 events.

- **Associations not explained by traditional RF or serum E2 levels**

- Results:
  - Frequent/persistent VMS associated with a 50-77% increased future CVD event risk

- Frequent VMS early in the MT or persistent VMS over the MT are associated with increased CVD events later in life
- More studies are needed

Thurston RC, et al. J Am Heart Assoc. 2021; 10(3): e017416.

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Females, VMS, and CVD

Menopausal Vasomotor Symptoms and Risk of Incident Cardiovascular Disease Events in SWAN (Study of Women's Health Across the Nation)

Rebecca C. Thurston, PhD; Helen E. Aslanidou Vlachos, MSc; Carol A. Derby, PhD; Elizabeth A. Jackson, MD, MPH; Maria Mori Brooks, PhD; Karen A. Matthews, PhD; Sioban Harlow, PhD; Hadine Joffe, MD, MSc; Samar R. El Khoudary, PhD, MPH

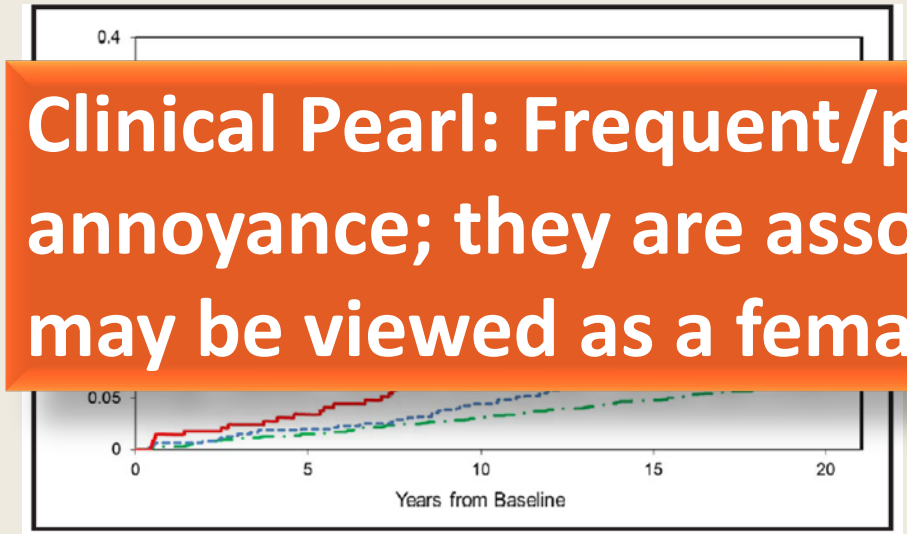

Figure 1. Baseline vasomotor symptoms (VMS) in relation to fatal and nonfatal cardiovascular disease (CVD) events, N=3083, 231 events.

Results

- Frequent/persistent VMS associated with a 50-77% increased risk of future CVD events

Clinical Pearl: Frequent/persistent VMS are more than an annoyance; they are associated with increased CV events and may be viewed as a female-specific CVD risk factor.

- **Associations not explained by traditional RF or serum E2 levels**

Thurston RC, et al. J Am Heart Assoc. 2021; 10(3): e017416.

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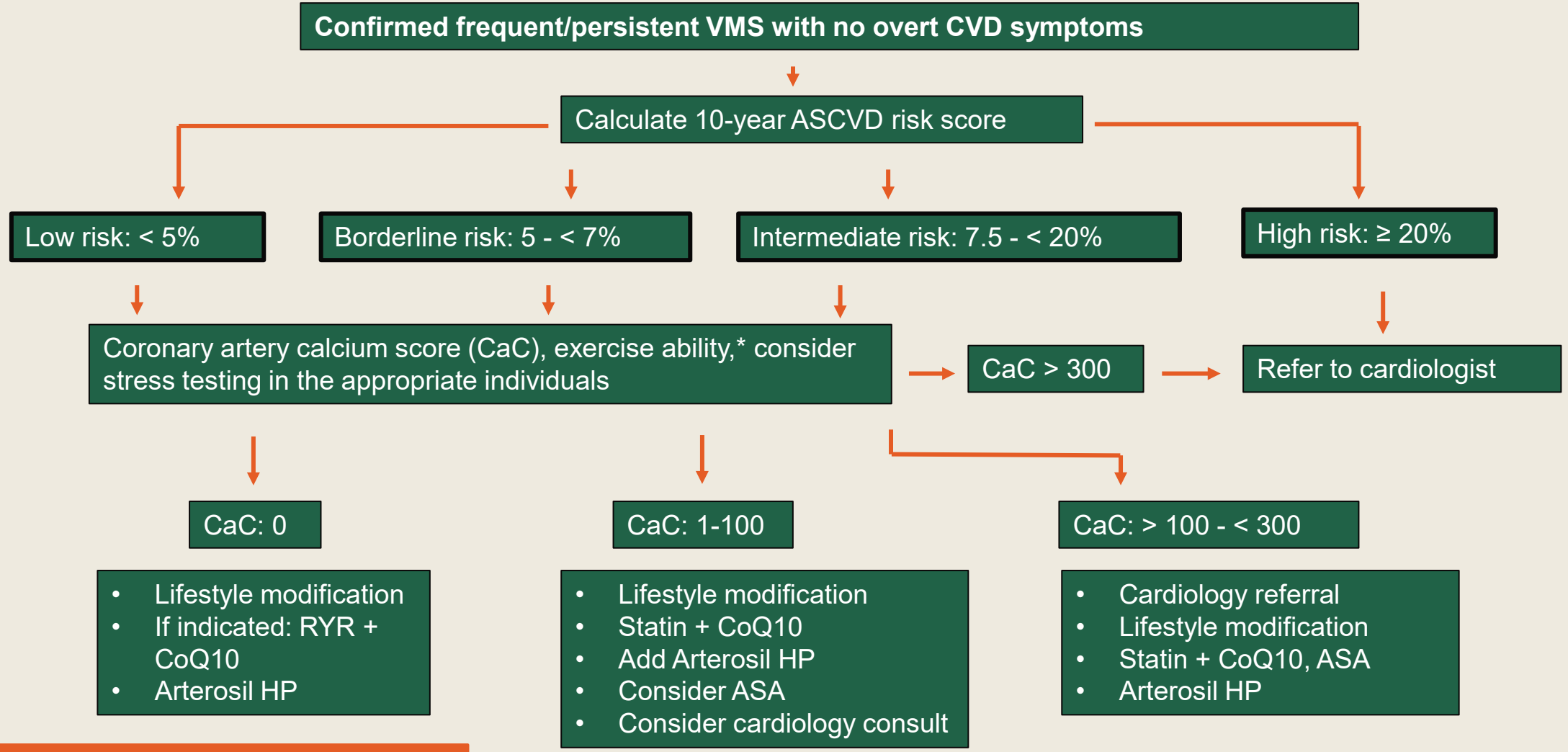

Sexual activity = walking 1 mile on a flat surface in 20 minutes, briskly climbing 2 flights stairs in 10 sec, or walking 4 min using the Bruce treadmill protocol

Adapted from: Miner M, et al. Sex Med Rev. 2019; 7(3): 455-463.
Gandaglia G, et al. Eur Urol. 2014; 65(5): 968-978.

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E2, Decreases CV Morbidity and Mortality

Studies	Study Drugs/Doses	Results
Studies documenting mixed results		
WHI	• CEE-alone (0.625mg/d) • Placebo	• PMP females 50-59: 40% decreased MI risk and all-cause mortality • PMP females 60-69: neutral effects on CV outcomes • PMP females 70-79: trend towards increased CV events
ELITE	• No uterus: O-E2 1mg/d • Yes, uterus: O-E2 1mg/d + VMP gel 45mg/d, days 1-10 • Placebo	• Two study groups: early (< 6 years PMP) and late (≥ 10 years PMP) with subclinical atherosclerosis (ASCVD) • PMP early group: o-E2 slowed CIMT progression compared to placebo, but only at 5-year follow-up • PMP late group: no difference in CIMT progression compared to placebo
ELITE post-trial analysis	• No uterus: O-E2 1mg/d • Yes uterus: O-E2 1mg/d + VMP gel 45mg/d, days 1-10 • Placebo	• On treatment serum E2 levels were differentially associated with CIMT progression according to timing of MHT initiation • Early PMP group: the higher the treatment serum E2 level, the slower the CIMT progression rate (serum E2: 48.2 ± 35.4pg/mL) • Late PMP group: with higher serum E2 levels, CIMT progression rate was increased (serum E2: 40.2 ± 23.6pg/mL)
Studies documenting no CV benefit and no harm		
KEEPS	• PREMARIN 0.45mg/d + PROMETRIUM 200mg/d x 12d • CLIMARA 0.05mg/d + PROMETRIUM 200mg/d x 12d • Placebo	• Naturally PMP females within 3 years of menopause, none with subclinical ASCVD • Neither PREMARIN nor CLIMARA affected the rate of CIMT progression after 4 years • PREMARIN: trend toward reduced CaC accumulation • Serum E2 on CLIMARA: mean 44pg/mL, average: ~ 40pg/mL
Studies documenting CV benefits		
DOPS	• No uterus: O-E2 2mg/d • Yes uterus: O-E2 2mg/d x 12d; O-E2 2mg + 1mg NORETHISTERONE ACETATE x 10d; o-E2 1mg/d x 6 days • Placebo	• Recently PMP, treated 16 years • All treatment groups had a significantly lower coronary heart disease risk at both 10- and 16-years of follow-up • At 10 years, PMP females receiving O-E2 had a significantly reduced CV event risk such as heart failure and MI
FINNISH-OS	• O-E2 1-2mg/d • TD E2 patches 0.025mg-0.1mg/d • TD E2 gels 1-2mg/d • Progestins used in PMP females with a uterus • Never users	• In all E2 users, CAD-related death risk was reduced by up to 54% in a time-dependent manner • The longer a females was prescribed and used an E2-based MHT, the greater the risk reduction • All risk reductions were comparable in PMP females initiating E2 < age 60 and in females initiating therapy ≥ 60 years or older

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Key Points: E2 and CVD Risk, FINNISH

- **Estradiol decreases CV morbidity and mortality up to 54%**
  - E2's CVD mortality reduction is positively related to E2 exposure time
  - TD E2 patches (0.025mg/d) and gels (1-2mg/d), and o-E2 (1-2mg/d) have been associated with decreased CV mortality
  - Treat females as early as possible, okay to initiate therapy later, and treatment may be continued for > 10 years, as long as there is ongoing risk stratification
  - Adding OMP 200 or 100mg/d or VMP 100 or 45mg/d does not increase CVD risk, may provide CVD benefits, while protecting the endometrium and improving BMD

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Key Points: E2 and CVD Risk, ELITE

- **Estradiol decreases CV morbidity and mortality**
  - Recently menopausal females, depending on CVD risk (those with subclinical ASCVD), may require higher serum LC-MS/MS E2 levels closer to the low luteal range (40-60pg/mL or validated dried-urine levels of ~ 1.8-2.0ng/mg) for CIMT reduction
  - Older PMP females or females further from menopause onset probably do best with serum LC-MS/MS E2 levels just outside the PMP range (20 to < 40pg/mL, goal ~ 30pg/mL or validated dried-urine levels of 0.7 to ~ 1.3 to 1.5ng/mg), regardless of CVD risk
  - Time since menopause and age > 60 should cause pause, not prevent MHT initiation or continuation
  - Ongoing risk stratification and follow-up testing is a must for all females

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Key Points: E2 and CVD Risk, ELITE

- Estradiol decreases CV morbidity and mortality
  - Recently menopausal females, depending on CVD risk (those with subclinical

Clinical Pearl: When counseling patients, remind them that currently estradiol is NOT indicated to prevent adverse cardiovascular outcomes; however, the data suggests that it will improve CVD outcomes and the earlier you initiate therapy the greater the benefits.

    initiation or continuation
  - Ongoing risk stratification and follow-up testing is a must for all females

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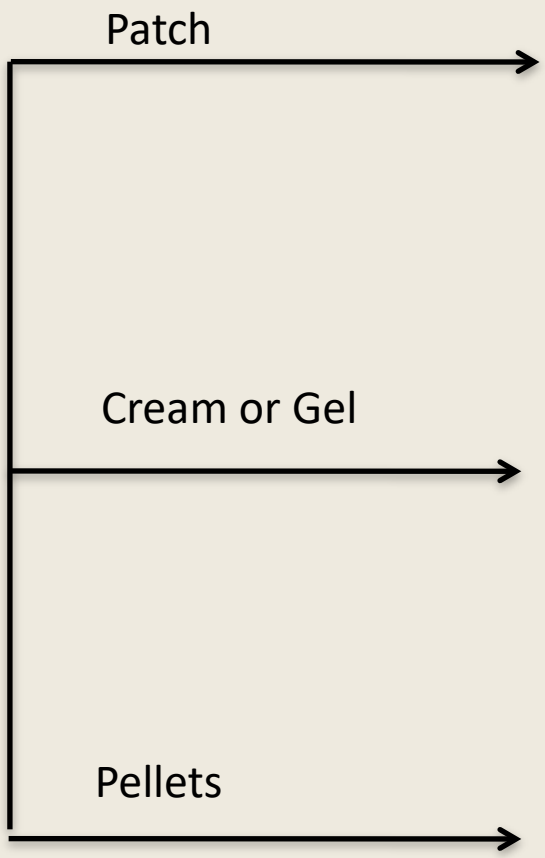
Estradiol Options



- **Estradiol patch**
  - Doses as low as 0.014mg/d relieves VMS, VVA symptoms, and prevents osteoporosis
- Place patch on a fatty area – abdomen or buttocks recommended
  - Buttocks gets increased absorption – FDA studies
- Labs in 12 weeks

- **Creams must be compounded, usually E2 and E3**
  - Typical ratios 80: 20, 50: 50
  - Common E2 starting dose is 0.50mg/day
    - Creams absorb < gels and patches, unless using vaginal application
- **Gel doses are product specific**
  - Not FDA-approved for osteoporosis prevention

- Not a good option for initial E2 delivery
- Would avoid in women with a uterus

- Must balance E2's proliferative effects with:
  - OMP 200mg, 100mg or VMP 100mg, 45mg daily

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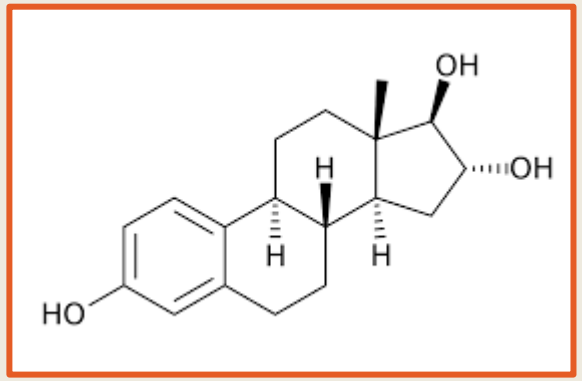
Estriol (E3)



en.wikipedia.org

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Estriol (E3)

- There are no FDA-approved E3 formulations, therefore, it must be compounded
- Radiolabeled studies indicate that E3 is predominantly formed from estrone (E1)
- E2 is reversibly oxidized to E1 and both E1 and E2 can irreversibly be converted to E3
- Androstenedione can also contribute to E3 formation
- In vitro studies document that E3, when given with E2, may exert antagonistic effects

Ali ES, et al. Menopause. 2017; 24(9): 1081-1085.

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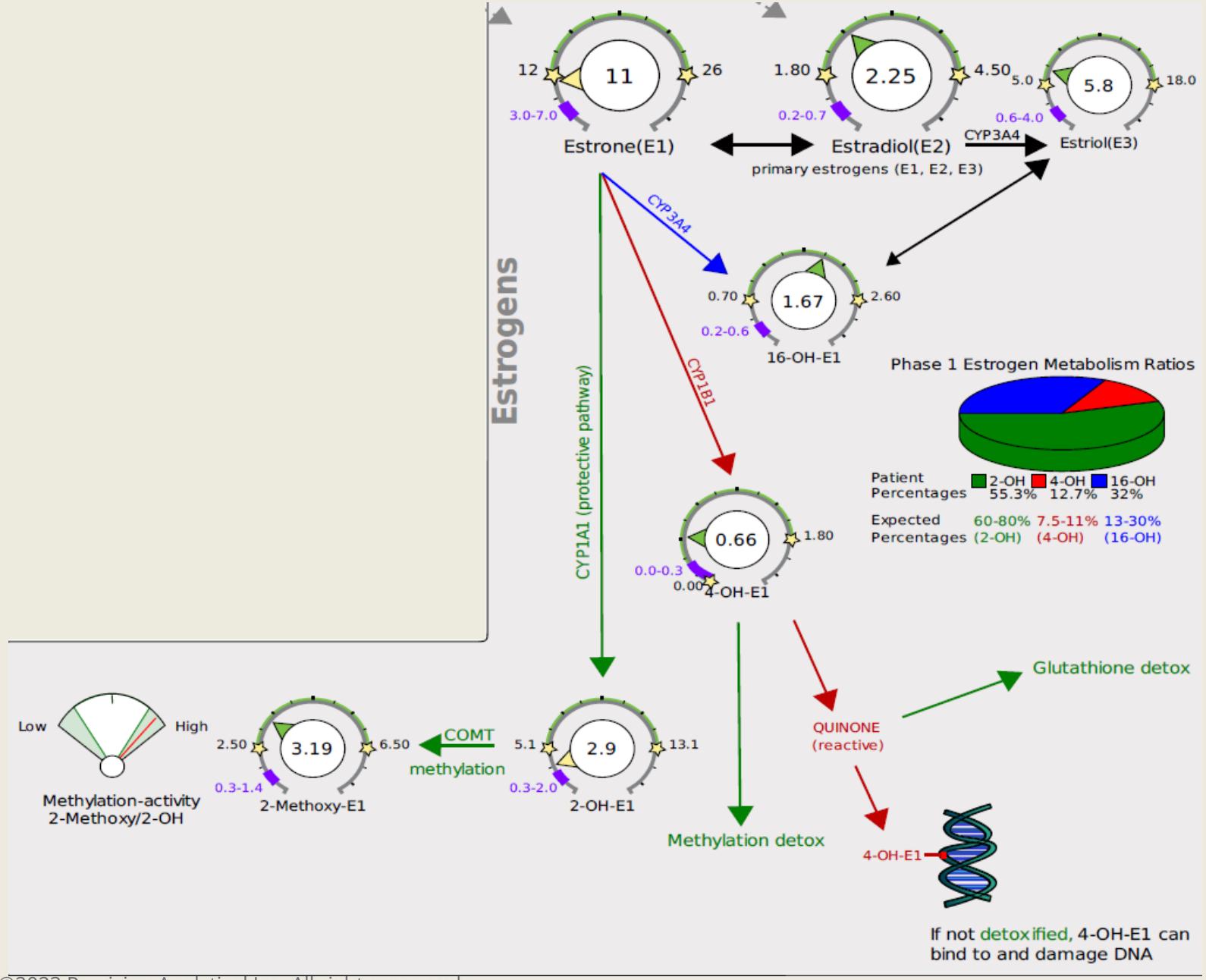

Estrogen Metabolism

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Estriol (E3): Clinical Utility

- **Menopause**
  - 40-50% of PMP females develop VVA signs and symptoms
  - Vaginal E3 (VE3): 0.5-1.0mg improves VVA symptoms
  - VE3 1.0mg had a greater effect on relieving VMS
- **Cancer**
  - Endometrial cancer: VE3 does not cause endometrial thickening or proliferation
  - BC: Mixed Data
    - Animal studies: E3 breast implantation reduced the development of chemically induced BC
    - In vitro BC cell line studies: E3 could bind to and stimulate BC in tissue culture
    - Human studies: physiologic E3 levels were not a significant BC protector

Ali ES, et al. Menopause. 2017; 24(9): 1081-1085.

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Estriol (E3): Clinical Utility

- **Immune modulator: Needs more studies**
  - May have potent immunomodulatory effects
    - Decreases proinflammatory cytokines, i.e., TNF-α, down-regulating NF-$\kappa\beta$, and upregulates anti-inflammatory cytokines, i.e., IL-10
  - Estrogens have an emerging neuromodulatory and neuroprotective role in multiple sclerosis (MS), particularly E3 (both men and women)
    - Significant improvement in relapsing remitting MS during 3rd trimester pregnancy when E3 levels highest
    - In human RCT over 24 months, o-E3 8mg/d + injectable glatiramer acetate 20mg/d (MS immunomodulatory drug) reduced relapse rates
- **BMD**
  - Data mixed

Ali ES, et al. Menopause. 2017; 24(9): 1081-1085.

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E3 Key Points and Practice Pointers

- Estriol must be compounded
- Most support its vaginal use for VVA and maybe VMS
- Potential role in MS (oral or transdermal E3) for both men and women
- No large studies documenting E3's role in breast protection, plausibility argument, since it binds to ER-β, which is antiproliferative
- VE3 dosing for vaginal dryness: 0.5mg/mL in a mucolox base, apply 1mL QHS x 2 weeks, then 2x week for 2 weeks, then PRN

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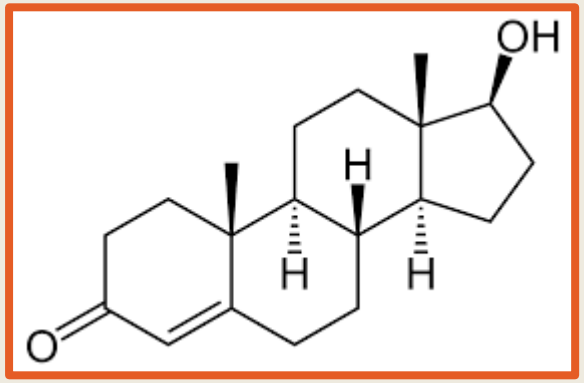
Testosterone (T)



en.wikipedia.org

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TTh in Females: The Guidelines

CONSENSUS STATEMENT

Global Consensus Position Statement on the Use of Testosterone Therapy for Women

Susan R. Davis,[1,A] Rodney Baber,[2,A,B] Nicholas Panay,[3,A] Johannes Bitzer,[4,C]

- **The only evidence-based indication for TTh is HSDD**
- **T in females should be monitored using LC-MS/MS**
- **Measure total testosterone (TT) and SHBG, less data on free T**
- **Uncertain association between TT levels and clinical findings**
- **No cutoff TT can be used to differentiate those with and without symptoms**
- **Approximate physiologic TT levels, no adverse effects**

Davis SR, et al. J Clin Endocrinol Metab. 2019; 104(10): 427-428.

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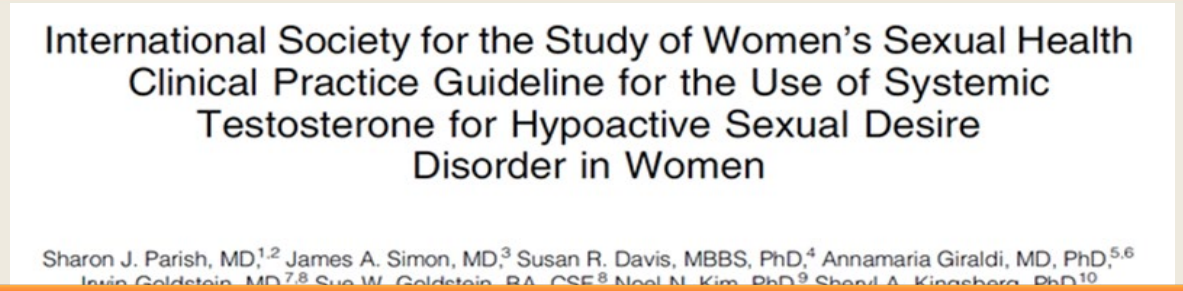
International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women

Sharon J. Parish, MD,[1,2] James A. Simon, MD,[3] Susan R. Davis, MBBS, PhD,[4] Annamaria Giraldi, MD, PhD,[5,6]

- **A clinical practice guideline for TTh in females including laboratory testing, dosing, post-treatment monitoring, and follow-up care**
- **TT not used to diagnose HSDD, but as baseline for monitoring**
- **Serum levels do not predict treatment efficacy**
- **Some correlation with treatment and response, bimodal curve where TT too high, sexual desire may decrease**
- **Serum LC-MS/MS trough testing done in 4-6 weeks to assess treatment efficacy, when stable Q4-6 months**

Parish SJ, et al. J Sex Med. 2021; 18(5): 849-867.

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TTh in Females: The Guidelines

International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women

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T Production in Females

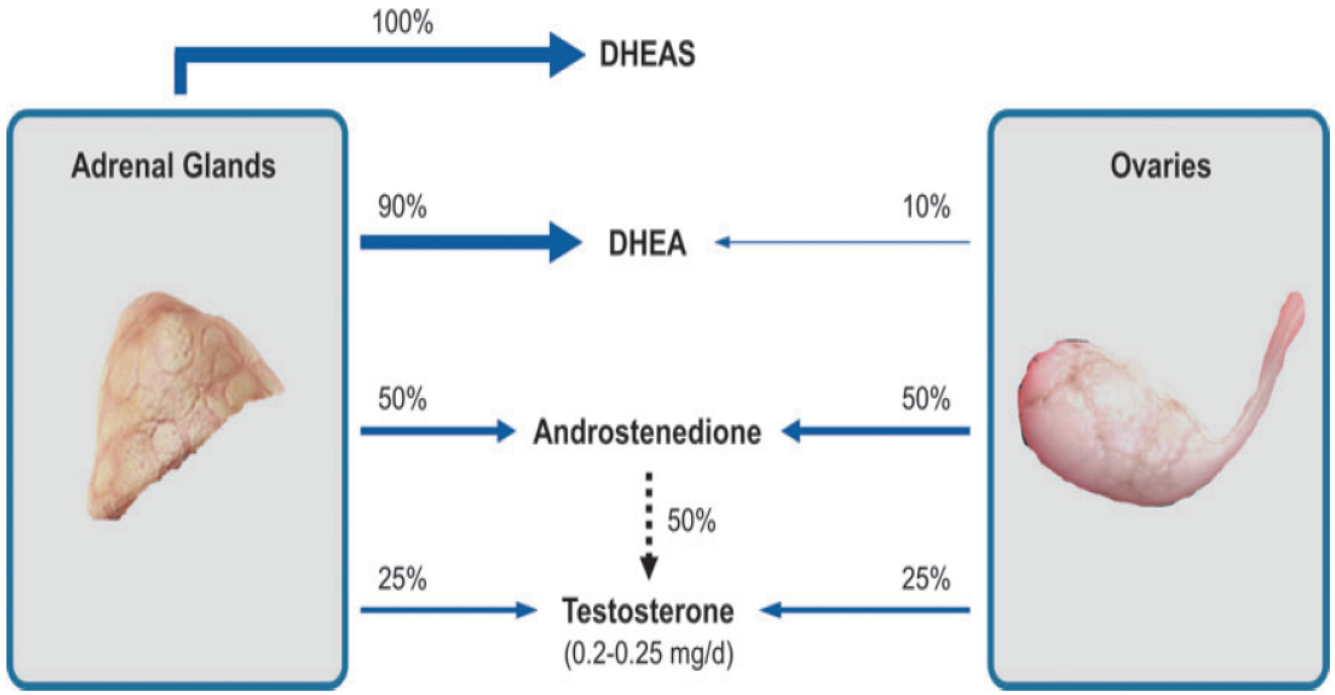

FIG. 1. Relative production of circulating androgens in the adrenal glands and ovaries. The substantial contribution of androstenedione to circulating testosterone is shown by a dashed arrow and involves peripheral tissue conversion. DHEA = dehydroepiandrosterone; DHEA-S = dehydroepiandrosterone sulfate.

Parish SJ, et al. J Sex Med. 2021; 18(5): 849-867.

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What Do We Know?

- Females synthesize ~ 0.2-0.25mg/d with mid-luteal levels ranging from 15-228ng/dL with a mean ~ 58ng/dL (LC-MS/MS)
- Dosing should be 1/10th to 1/15th a male dose: Typical male T gel dose = 50mg/d: 3.5-5.0mg/d to maintain physiologic levels
- Most T studies document that serum total T, FT, and bioavailable T levels at the high end of the RR are important for improved clinical success
  - T patch: 0.3mg/d; T gel: up to 10mg/d or 50mg/week; T cream: up to 10mg/d; T pellets: 1.0mg/kg every 3-4 months or ~ 75mg/Q3-4 months

Davis SR, et al. J Clin Endocrinol Metab. 2019; 104(10): 4660–4666.
Parish SJ, et al. J Sex Med. 2021; 18(5): 849-867.

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TTh in Females: Improves Clinical Outcomes

- **TD/vaginal/pellet T therapies improve symptoms AND clinical outcomes at serum levels ≥ upper limit of the reference range**
  - TTh when added to E2 and Pg improves BMD and endothelial function to a greater extent than E2 and Pg alone
  - TTh improves sexual function, VMS, and VVA (may be due to E2 aromatization)
  - TTh DOES NOT increase EC, CVD risk, BC, and may decrease BC incidence
- Studies that documented clinical success with serum TT levels that were somewhat or many times higher than the ULN, found no significant adverse events

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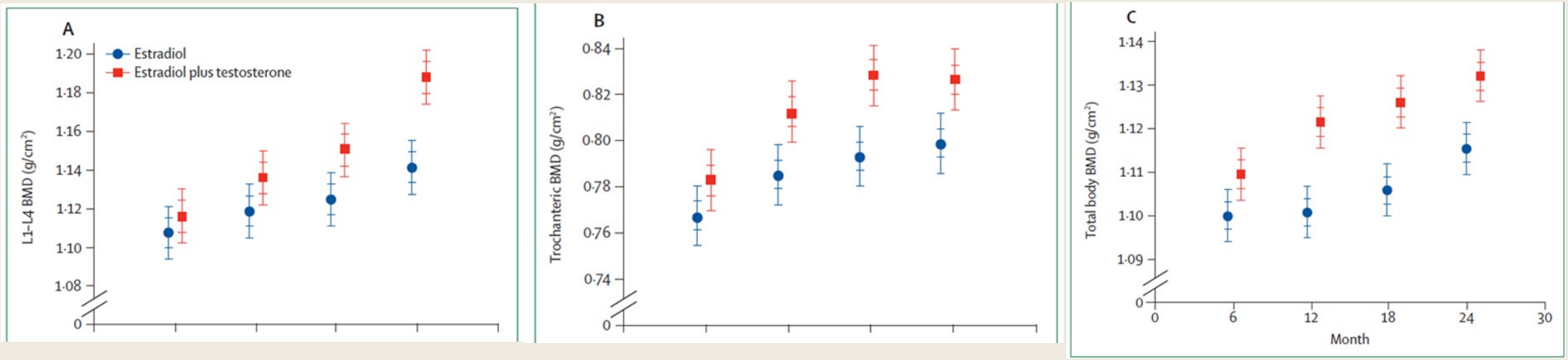
TTh Improves BMD



- **Study:** 34 PMP females, 2-year RCT (no placebo) evaluating androgens effect on BMD and libido; Immunoassay
  - Study drugs: E2 50mg pellet alone or an E2 50mg + T 50mg pellet Q 3mo
  - Mean serum TT levels ranged from **29-81ng/dL** throughout, mean E2 levels ranged from **~ 100-205pg/mL** (note: multiple E2 and T pellet doses withheld due to high serum levels; progestins given to females with a uterus)
- **Results:** Both E2 alone and E2 + T increased BMD, however, the **E2 + T group had a greater increase in BMD than E2 without T**
- **Conclusion: Adding TTh to E2 + Pg (in this case a progestin) more effective at increasing BMD than E2 + Pg alone**

Davis SR, et al. Maturitas. 1995; 21(3): 227-236.
Davis SR, et al. Lancet Diabetes Endocrinol. 2015; 3(12):980-992.

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TTh Improves Endothelial Function

Evidence That Parenteral Testosterone Therapy May Improve Endothelium-Dependent and -Independent Vasodilation in Postmenopausal Women Already Receiving Estrogen

SAMANTHA WORBOYS, DIMITRA KOTSOPOULOS, HELENA TEEDE, BARRY McGRATH, AND SUSAN R. DAVIS

The Jean Hailes Foundation (S.W., S.R.D.), Clayton 3168, Vic; and Department of Vascular Medicine (D.K., H.T., B.M.), Monash University, Clayton, Vic, Australia

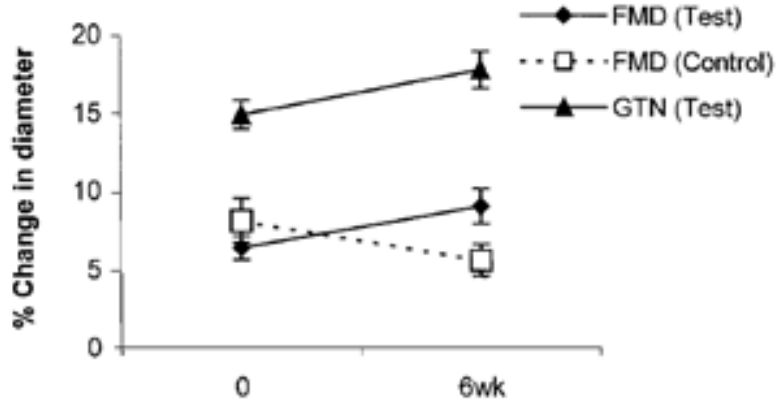

FIG. 1. Mean (±SEM) FMD- and GTN-mediated vasodilation in testosterone-treated women and mean FMD in controls, expressed as percentage change in vessel diameter.

- **TTh improves endothelial function in females on stable E2 (2001)**
  - **First RCT** to assess TTh's effect (T pellet 50mg) in females on stable E2 therapy (50mg pellet) for ≥ 6 months; baseline studies pre-treatment and 6-weeks post treatment
  - Results: 33 treated females vs 15 non-MHT users
    - TTh SS improved FMD (42% increase) and smooth muscle vasodilation when compared to PMP females not using MHT
    - TT levels SS different from baseline to 6-weeks
      - Baseline: **28.5 ± 2.3ng/dL;** 6-weeks: **144 ± 8.6ng/dL**
    - E2 levels not SS different from baseline to 6-weeks:
      - Baseline: 112.2 ± 12.8pg/mL; 6-weeks: 130 ± 15.8pg/mL
  - **Conclusion: TTh, when added to E2, further improves endothelial-dependent (FMD) and endothelial-independent (vascular smooth muscle) vasodilation, as well as BMD**

Davis SR, et al. Maturitas. 1995; 21(3): 227-236.
Worboys S, et al. J Clin Endocrinol Metab. 2001; 86(1): 158-161.

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TTh and Breast Cancer (BC)

- **T is breast protective and does not increase BC**
  - T is antagonistic to E2, inhibits ER-α, prevents E2 stimulation, and decreases breast proliferation if aromatization is controlled
  - AR signaling exerts a pro-apoptotic, anti-estrogenic, growth inhibiting effect on normal and cancerous breast tissue
  - BC's, which are AR (+) are associated with a better prognosis
  - It is the T/E2 ratio, or the balance of these hormones that is breast protective
  - T + an aromatase inhibitor (combined in a pellet) has been shown to not only decrease androgen deficiency symptoms in BC survivors, but to decrease invasive BC incidence, and decrease tumor size when implanted directly in the breast

Dimitrakakis C, et al. Menopause. 2004; 11(5): 531-535.
Glaser RL, Dimitrakakis C. Maturitas. 2013; 74(3): 230-234.
Glaser RL, Dimitrakakis C. Maturitas. 2015; 82(3): 291-295.
Glaser RL, et al. BMC Cancer. 2019; 19(1): 1271.

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TTh and Breast Cancer: The Dayton Study

Table 4 Incidence rates of IBC, comparison to published studies

	Cases per 100,000 p-y	Years Observed
Dayton Study		
T, T + AI	165	10
WHI RCT [29,30]		
Placebo	330	10.7
E alone	260	10.7
E + P	380	5.2

- Objective: 10-year prospective cohort study, assessing the long-term BC incidence in females treated with T pellets for hormone deficiency symptoms
- Study: 1267 pre/perimenopausal (23.2%) and PMP (76.8%) females, mean age 52.1 treated with T pellets or T + A pellets, 119 served as pseudo-control group
- Results: BC incidence compared to historical controls and age-matched Surveillance Epidemiology and End Results Data (SEER)
  - 39% decrease in invasive BC when compared to age-matched SEER data
    - T or T + A: 165/100,00 person-years vs SEER 271/100,00 person-years ($P < 0.001$)
  - T or T + A: 165/100,00 patient years vs "pseudo-control group:" 390/100,000 person-years ($P < 0.001$)
- **Conclusion: Long-term treatment with T implants did not increase invasive BC incidence, and should be investigated for hormone therapy and BC prevention**

Glaser RL, et al. BMC Cancer. 2019; 19(1): 1271.

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Testosterone Options

Topical, usually a cream

- Typically compounded
- Starting dose can range from 0.5 up to 5mg/d

Vaginal

- Typically compounded
- Lower 1/3 vagina/labia
- Starting dose range: 0.25-2.5mg/d

Pellets

- An excellent option
- Must understand hormone metabolism and detoxification
- Starting dose range: 1.0mg/kg/3-4 months, or ~ 75mg Q3-4 months
- Patients require less T than you think!

- Monitoring after 12 treatment weeks
  - Blood
  - Urine for comprehensiveness

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Key Points

- E2, Pg, and T improve clinical outcomes
- Estradiol improves VMS, VVA, BMD, decreases BC and CV mortality; cognition data is mixed
- Pg is estradiol's physiologic partner, is necessary to balance E2's proliferative effects, and maintain optimal BMD
- Testosterone improves VMS, VVA, BMD, endothelial function, and may have a role in decreasing BC

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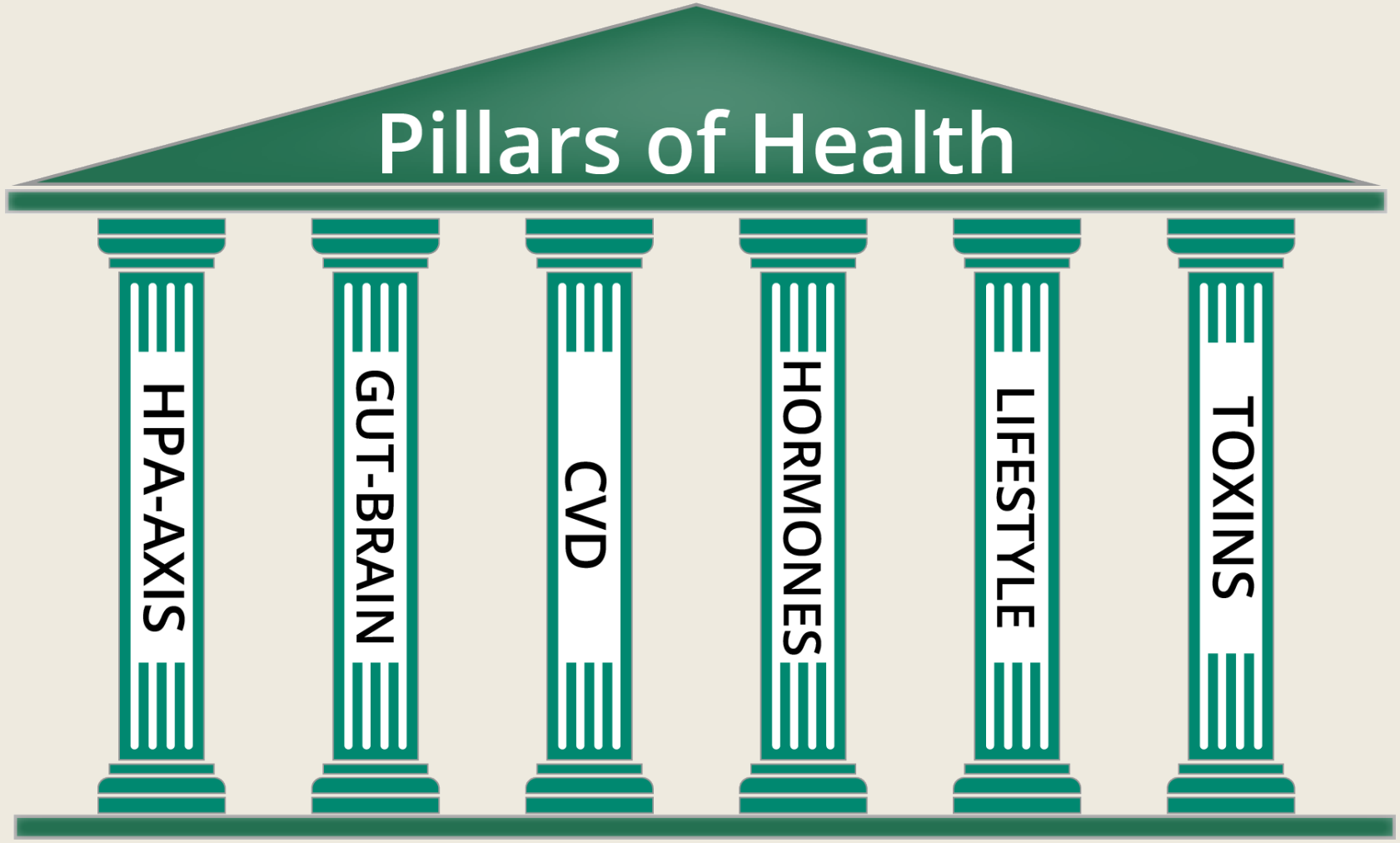
Risk Factors Matter



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Females may spend ~ 1/3 of their life hormone insufficient/deficient, so it's important we get it right!

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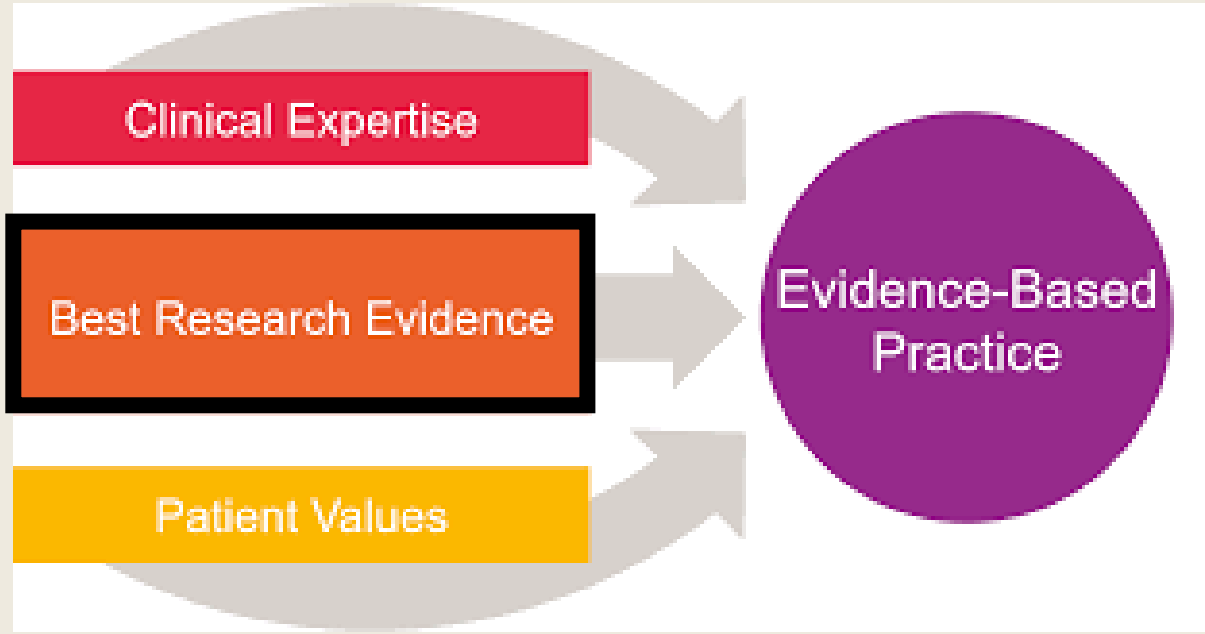
Questions?



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