BHRT: Clinical Benefits and Outcome Studies

Doreen Saltiel, MD JD FACC FAARM ABAARM

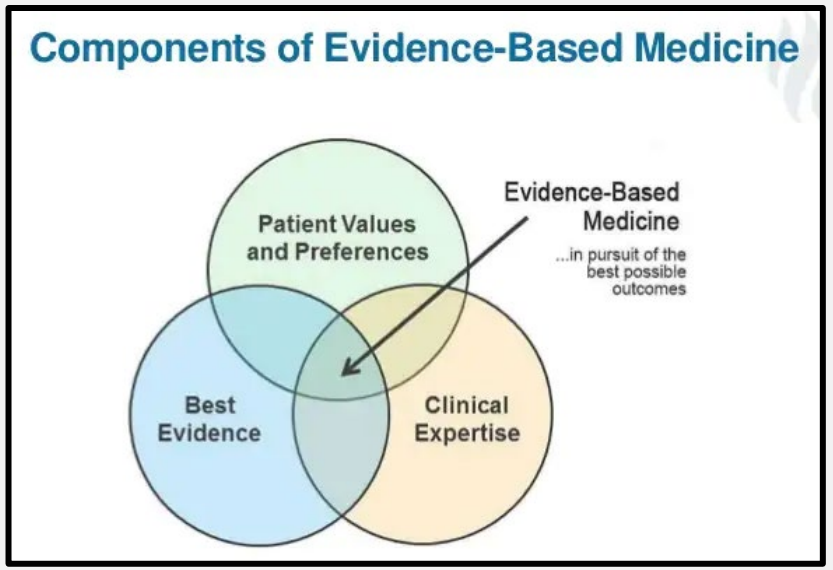
Evidence based Medicine: EBM

- **Definition:**

„…the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients"

Sackett et al. Brit. Med. J. 1996, 312: 71

slideshare.net



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Disclosures

- Member: ACC's CardioServe Research Panel
- Speaker: Calroy Health Sciences
- Consultant: Precision Analytical Inc.

Evidence That Changed My Practice

- In PMP women, serum or validated DUTCH levels between the postmenopausal and luteal ranges can be used to monitor TD E2; however, DUTCH, a validated, peer-reviewed 4-spot dried urine test is a better option
- TD Pg (non-vaginal) DOES NOT balance E2's endometrial proliferative effects
- In women, TD T doses as high as 10mg/d and pellet doses (50-150mg) that increase serum T 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
- There are NO outcome studies using compounded creams

Key Point

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

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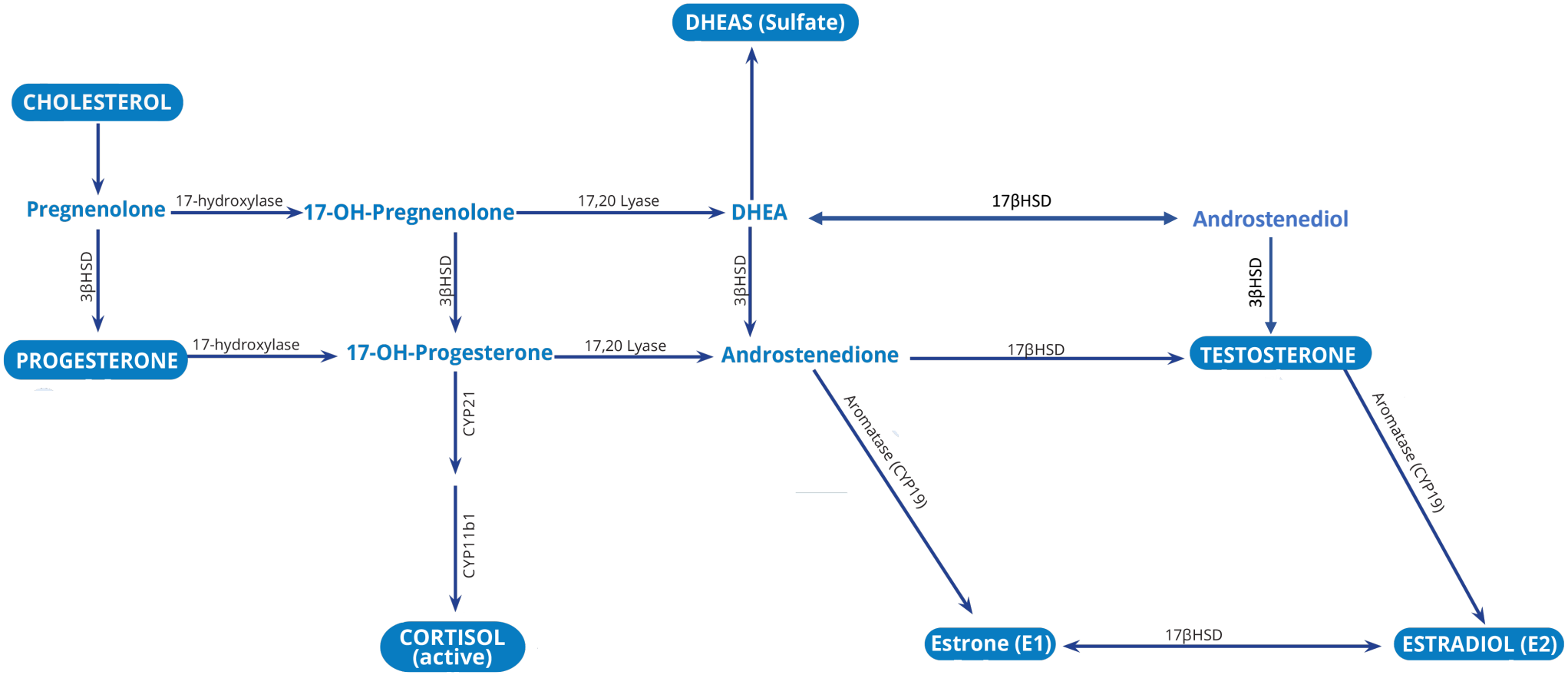
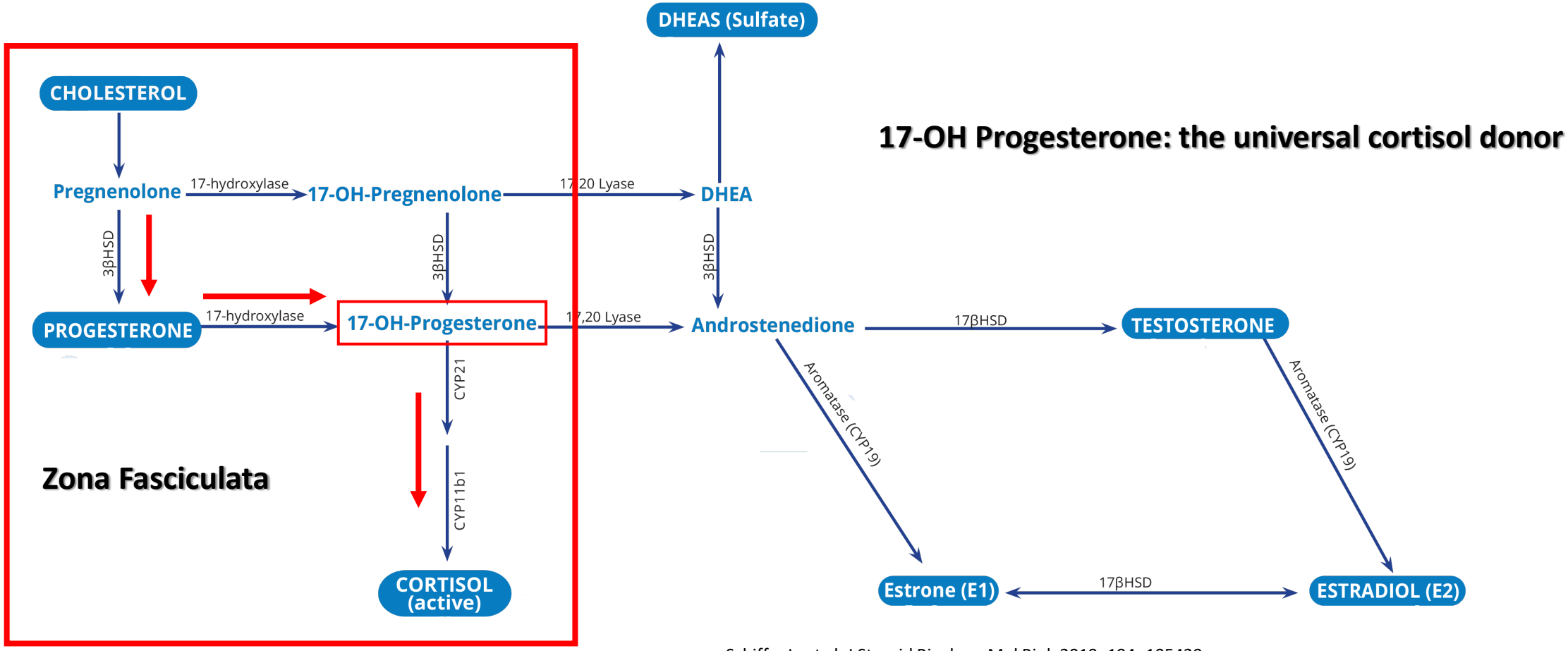
Objectives

- 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
  - The limitations of hormone-related guidelines

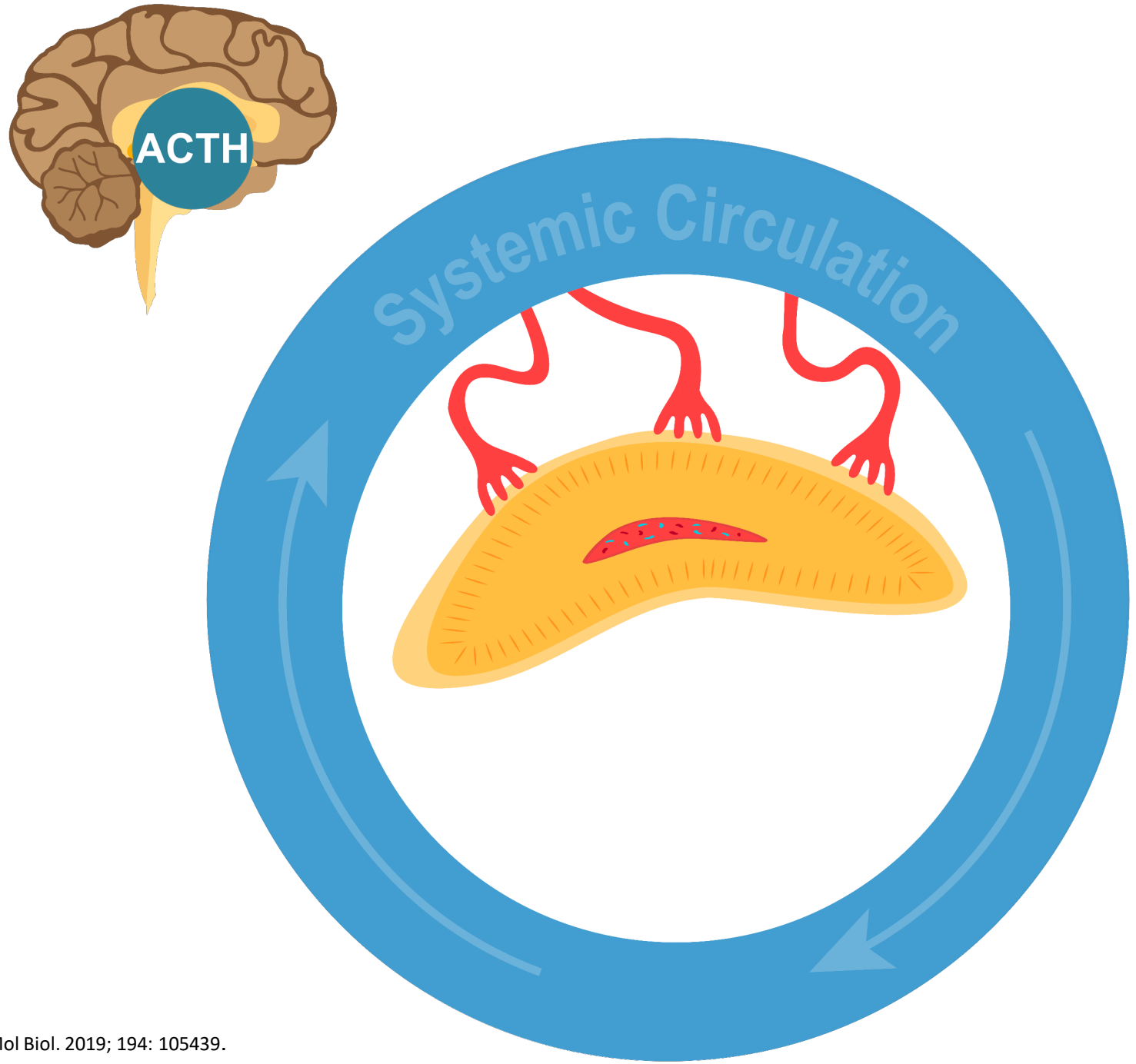
Steroid Pathway



There is NO “Pregnenolone or Progesterone Steal”



Schiffer L, et al. J Steroid Biochem Mol Biol. 2019; 194: 105439.



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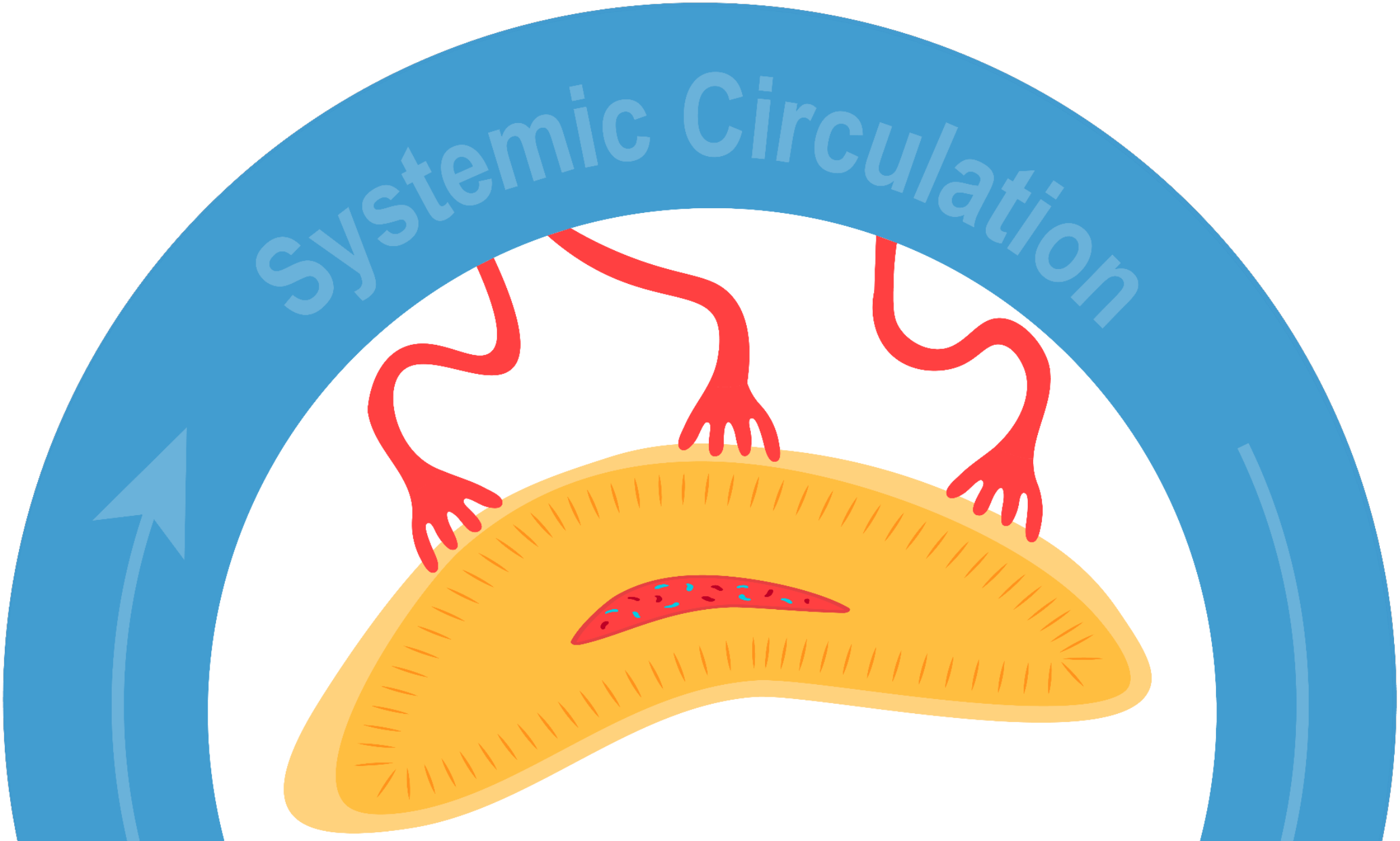
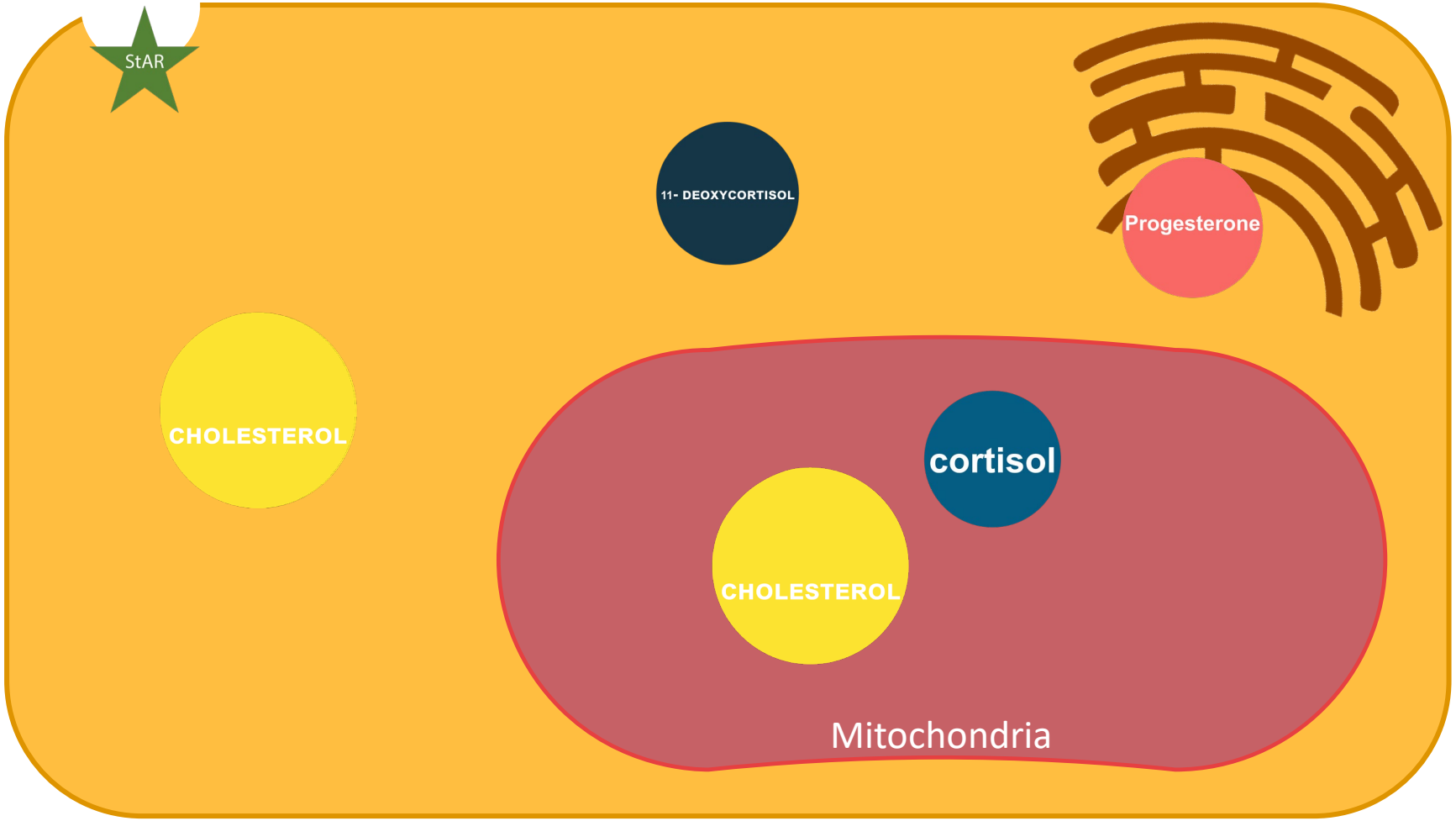
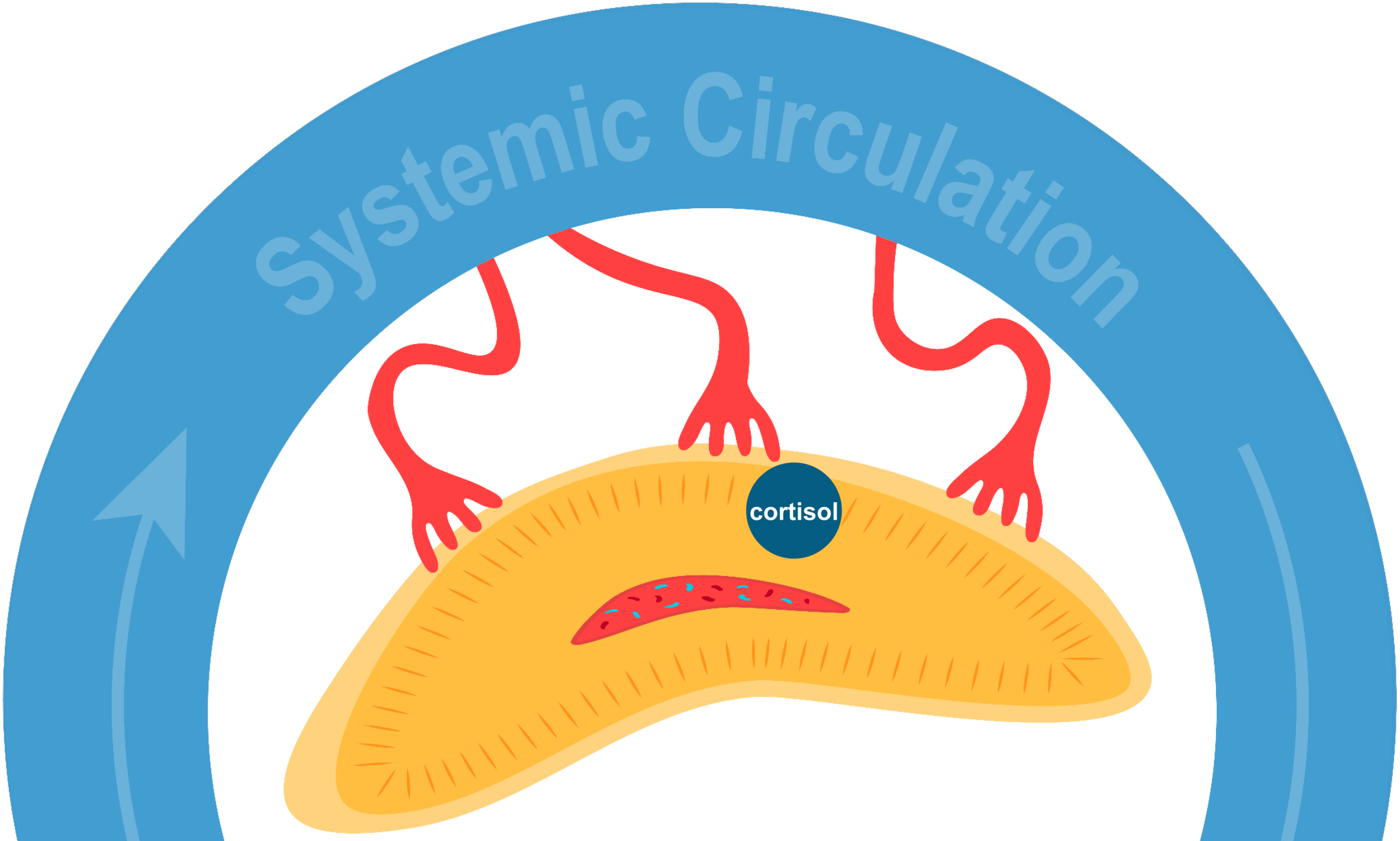

Systemic Circulation

Adrenal Cortex Cell




Systemic Circulation
cortisol

Key Questions

1. Why do we prescribe hormones?
2. What hormones should we prescribe?
   - What doses and delivery methods does the evidence support?
3. Why do we test hormones?
4. What tests do we do?

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Why Do We Prescribe Hormones?

Improve Clinical Outcomes

Pre/perimenopausal Women

- Luteal phase defects
  - Adolescents
  - Reproductive women
- Perimenopause

PMP Women

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

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

Key Questions

1. Why do we prescribe hormones?

2. What hormones should we prescribe?

- What doses and delivery methods does the evidence support?

3. Why do we test hormones?

4. What tests do we do?

Questions

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

Dose and Delivery Method?

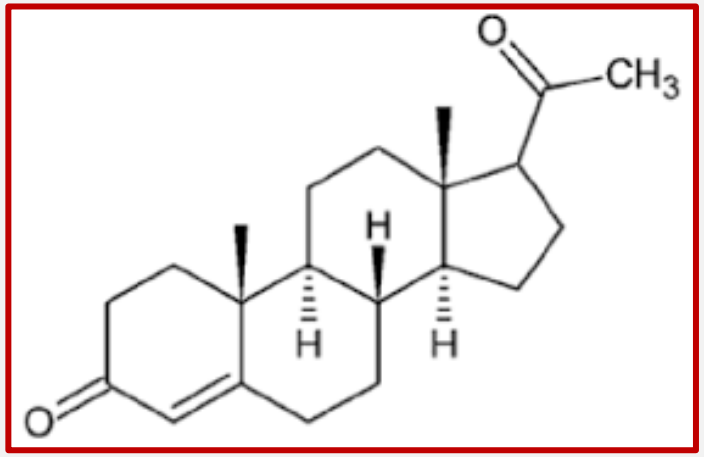
- What does the literature tell us about MHT (Pg, E2, and T) dosing, delivery, and clinical outcomes?

- What levels have been documented to be safe and improve clinical outcomes?

Today's Outline For Each Hormone

- Discuss relevant guideline and where they fall short
- Discuss agreed upon benefits of each hormone, including delivery and dosing
- Discuss benefits that are somewhat controversial
- Discuss how to use each hormone in clinical practice

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 the use of 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

Progesterone Guidelines

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- When the use of progestero[illegible]ry, [oral] micronized progesterone is considered a safer alter[illegible]
- Oral micronized pr[illegible]rotects 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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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
- 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
      - Women with baseline E2 ≥ 10pg/mL were more likely to have a baseline proliferative endometrium than women with a baseline E2 < 5pg/mL or in the 5 to < 10pg/mL range

Oral Micronized Progesterone (OMP) and the Endometrium

- OMP 200mg protects the endometrium
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Clinical Pearl: A woman's endometrial health pre-hormone initiation is key when determining initial OMP and TD E2 doses.

  - Gillet (OS, 1994): OMP 100mg continuous + Oestrogel 1.5mg
  - DiCarlo: (OS, 2010): 100mg x 12 days + 0.05mg patch
  - Mirkin: (RCT, 2020): REPLENISH: 100mg + 1mg oral E2 in a combination capsule
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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

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	• Women who wished a monthly cycle: OESTOGEL 3.0mg (days 1-25) + UTROGESTAN 300mg (days 16-25) • Women 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 woman
		  ○ Endometrial proliferation in 2.9%
		• E2 0.50mg/d + 50mg OMP capsule @ 1 year
		  ○ Endometrial proliferation in 0.3%

Pg and Endometrial Studies

TD Pg and the Endometrium

makeameme.org

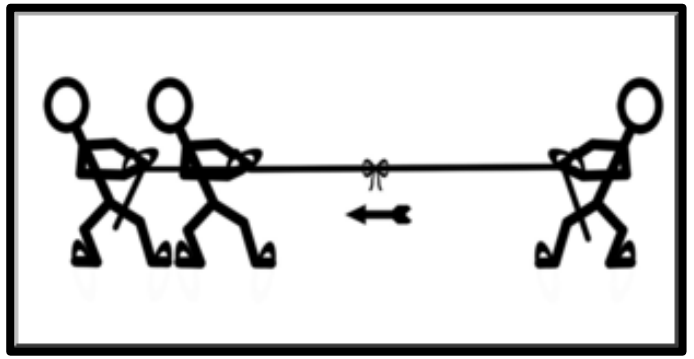
TD Pg: Not Recommended for Endometrial Protection

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's endometrial effects
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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.

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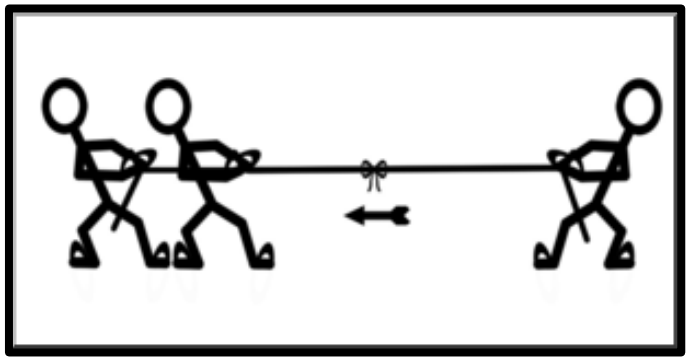


Wren B. Med J Aust. 2005; 182(5): 237-239.

Key Points: Pg and the Endometrium

- A woman'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

Micronized Progesterone's (Pg's) Benefits

Benefits

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

Potential Benefits

- Neurobiological effects

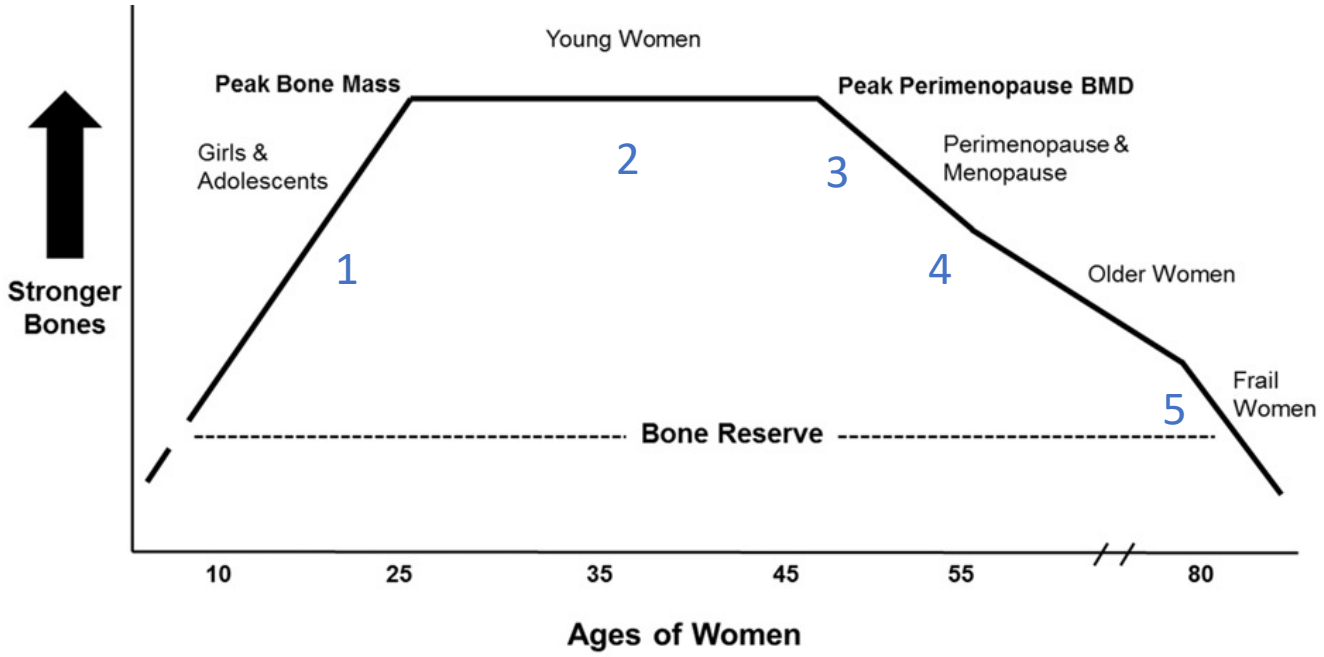
Safety Issues

- Safe for the CV system
- Safe for the breast

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 women
  - Adolescents, premenopausal women, and perimenopausal women 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

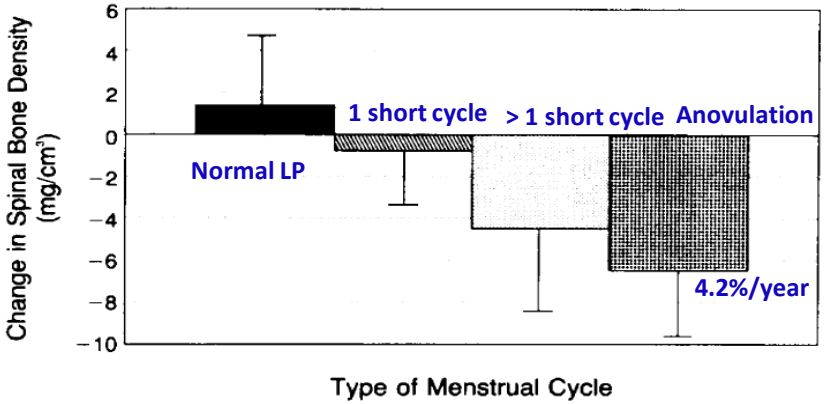
Adapted from: Prior JC. Climacteric. 2018; 21(4): 366-374.

Pg and Bone Mineral Density (BMD)

Volume 323 NOVEMBER 1, 1990 Number 18

SPINAL BONE LOSS AND OVULATORY DISTURBANCES

JERILYNN C. PRIOR, M.D., YVETTE M. VIGNA, B.A., R.N., MARTIN T. SCHECHTER, M.D., M.SC., PH.D., AND ARTHUR E. BURGESS, PH.D.



- Objective: 1-year study assessing spinal bone loss in 66 premenopausal women, ages 20-42, QCT used to assess BMD
- Results: No SS difference in the change in BMD between normal LP women and in those with one short cycle: stable BMD; There was a SS difference between the women with normal LP and only 1 short cycle vs the women with either > 1 short cycle or anovulation ($P < 0.0001$)
- **Conclusion: Even in the presence of normal E2 levels, > 1 short luteal cycle and any anovulatory cycles increase risk for early and possibly excess bone loss**

Negative Spinal Bone Mineral Density Changes and Subclinical Ovulatory Disturbances—Prospective Data in Healthy Premenopausal Women With Regular Menstrual Cycles

Danni Li, Christine L. Hitchcock, Susan I. Barr, Tricia Yu, and Jerilynn C. Prior*

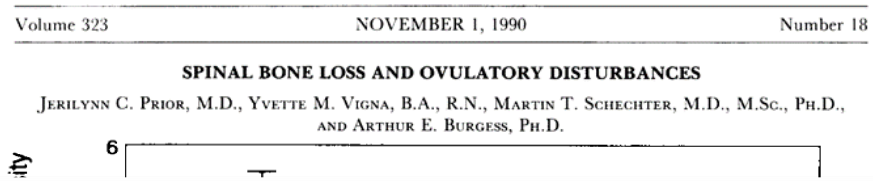
* Correspondence to Dr. Jerilynn C. Prior, Centre for Menstrual Cycle and Ovulation Research, Department of Medicine/Endocrinology, University of British Columbia, 2775 Laurel Street, Suite 4111, Vancouver, BC, Canada V5Z 1M9 (e-mail: Jerilynn.prior@ubc.ca).

- Objective: Evaluate the relationship between subclinical ovulatory disturbances and BMD changes
- Study: 2014 meta-analysis of prospective studies involving 456 healthy women, ages 18-42
- Results:
  - Regularly menstruating women with more frequent ovulatory disturbances were losing BMD at ~ 1%/year (-0.86%/year)

- **Key Point: If a woman does not increase BMD as expected, or loses BMD at ~ 1%/year, over her 30-45 cycling years, it is possible that when she reaches perimenopause, she may already have lost 10-20% of her BMD**

Prior JC, et al. N Engl J Med. 1990; 323(18): 1221-1227.
Li D, et al. Epidemiol Rev. 2014; 36: 137-147
Prior JC. Climacteric. 2018; 21(4): 366-374.

Pg and Bone Mineral Density (BMD)



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

- Objective: 1-year study assessing spinal bone loss in 66 premenopausal women, 66 women 20-42, QCT used to assess BMD
- Results: No SS difference in the change in BMD between normal LP women and in those with one short cycle: stable BMD; There was a SS difference between the women with normal LP and only 1 short cycle vs the women with either > 1 short cycle or anovulation ($P < 0.0001$)
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(-.86%/year)

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Pg, BMD, and Treatment

- Adolescent and Reproductive age women
  - Address the HPA axis and all other underlying potential etiologies
  - OMP 300mg days 14-27 with oligomenorrhea and 14 days on and 14 days off with amenorrhea
- Perimenopausal and PMP women
  - There are no outcome studies evaluating progesterone alone regarding BMD and fracture risk in perimenopausal and PMP women
  - Prior et al., in 2017 published a RCT meta-analysis that included more than 1000 women; PMP women (~ 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)

Pg and Bone Mineral Density (BMD): Treatment

- Adolescent and Reproductive age women

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

0.0625mg/d), or CEE + mainly a progestin medroxyprogesterone 2.5mg/d

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

Micronized Progesterone's (Pg's) Benefits

Benefits

- Endometrial protection
- Optimizing BMD
- Vasomotor symptoms
- Sleep

Potential Benefits

- **Neurobiological effects**

Safety Issues

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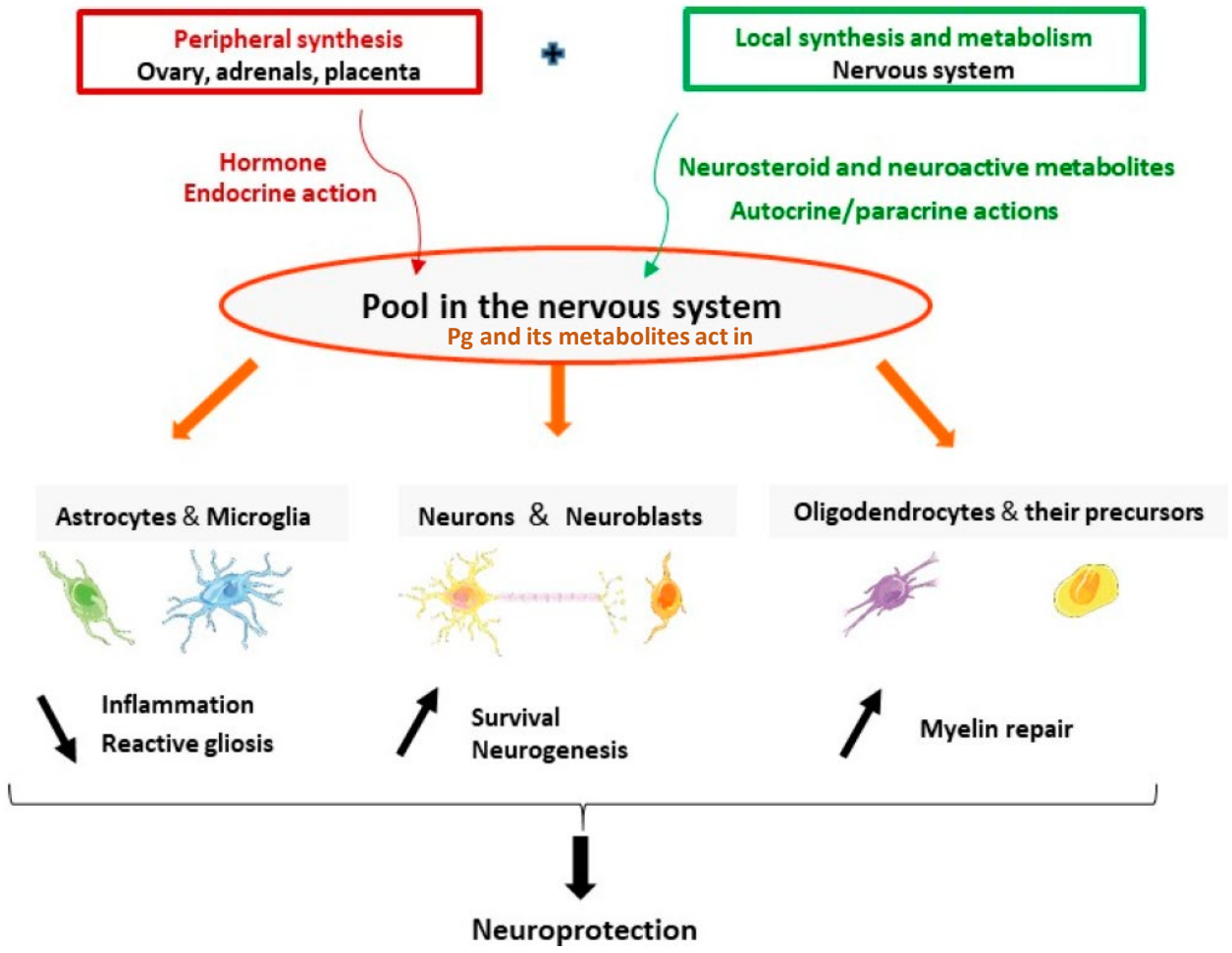
Pg as a "Plausible" Neuroprotectant



Guennoun R. Int J Mol Sci. 2020; 21(15): 5271.

- Pg is synthesized and metabolized in the brain
- Pg and its neuroactive metabolites, either synthesized in endocrine glands or locally in the nervous system, have pleiotropic neuroprotective effects

Distinct cognitive effects of estrogen and progesterone in menopausal women

Alison Berent-Spillson[a,*], Emily Briceno[b], Alana Pinsky[c], Angela Simmen[d], Carol C. Persad[b], Jon-Kar Zubieta[a], Yolanda R. Smith[d,**]

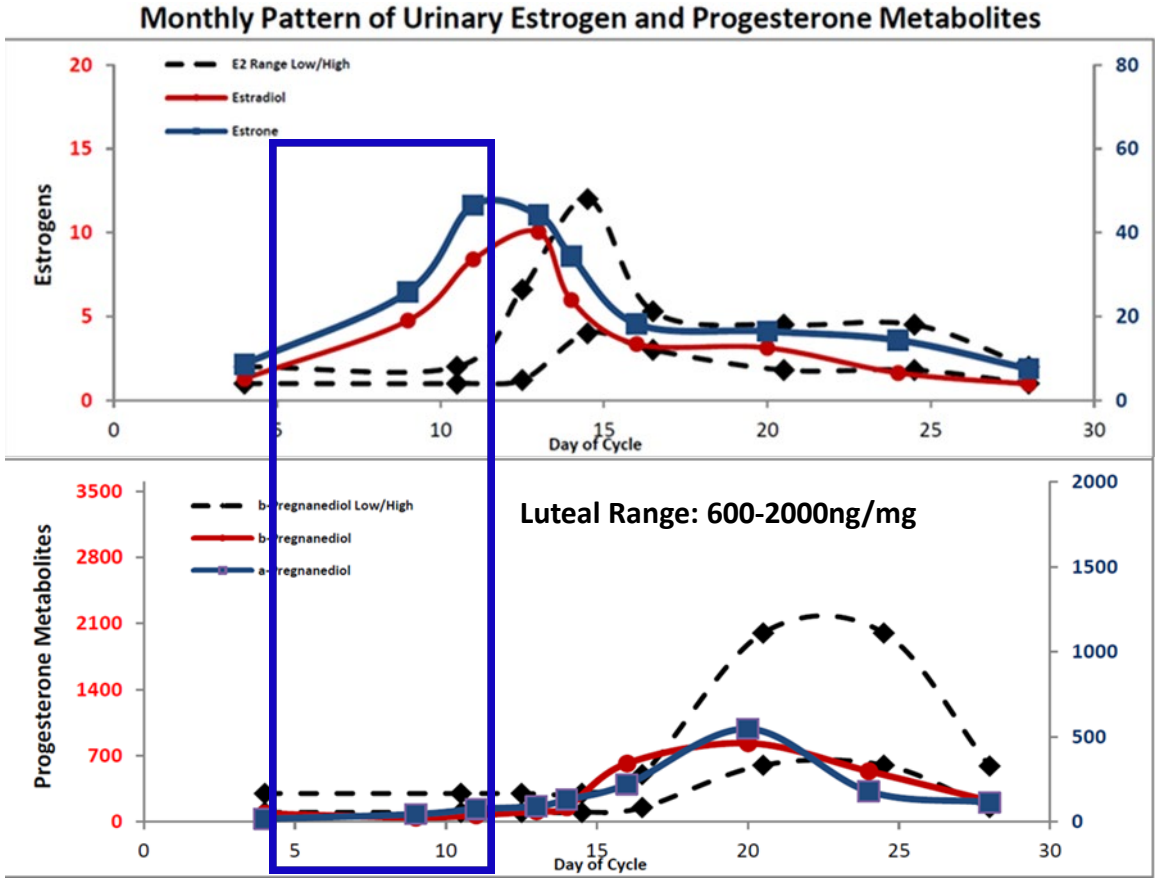
- Objective: To evaluate o-E2's (1mg) and OMP's (200mg) cognitive and neurobiological effects
- Study: 12-week RCT cross-over study involving 29 recently PMP women
  - O-E2: 16 women
  - OMP: 13 women
- Results: Both o-E2 and OMP were associated with verbal processing activation patterns. Compared to placebo:
  - O-E2: improved verbal processing
  - OMP: improved verbal memory tasks
- **Conclusion: Understanding E2's and Pg's effects could lead to more effective therapies that may impact cognitive performance**

Berent-Spillson A, et al. Psychoneuroendocrinology. 2015; 59: 25-36.

How do we translate this into clinical practice?

Low Pg, LDPs, and DUTCH Cycle-Map Testing

Baseline Cycle Map



Schiffer L, et al. J Steroid Biochem Mol Biol. 2019; 194: 105439.

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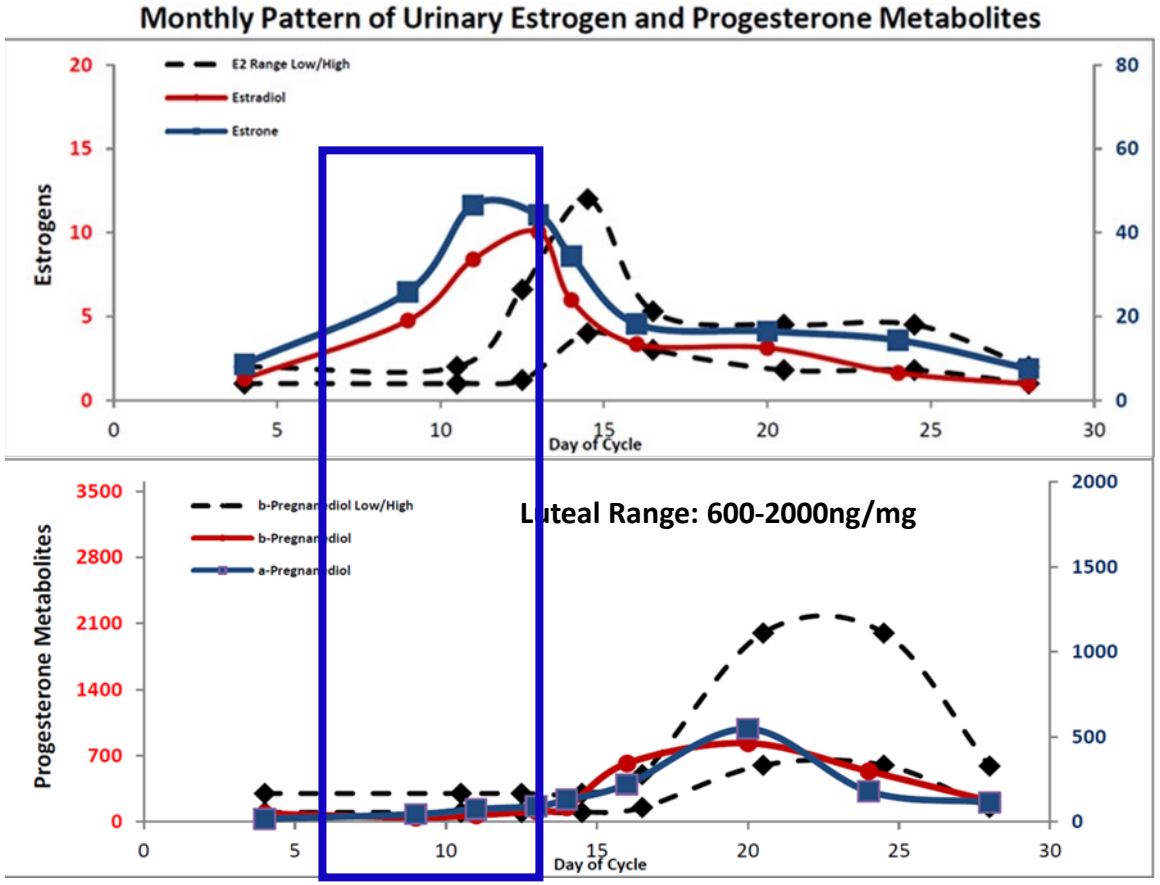
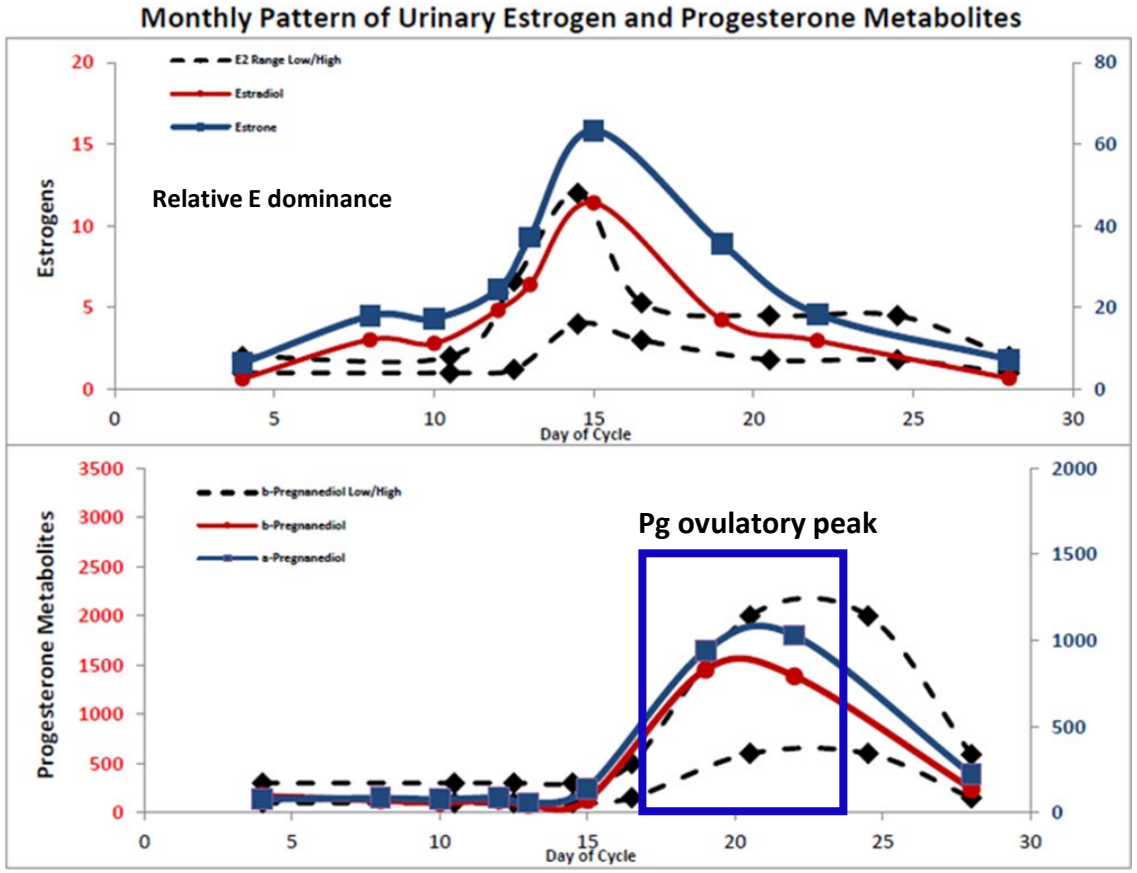


FU Cycle Map



Schiffer L, et al. J Steroid Biochem Mol Biol. 2019; 194: 105439.

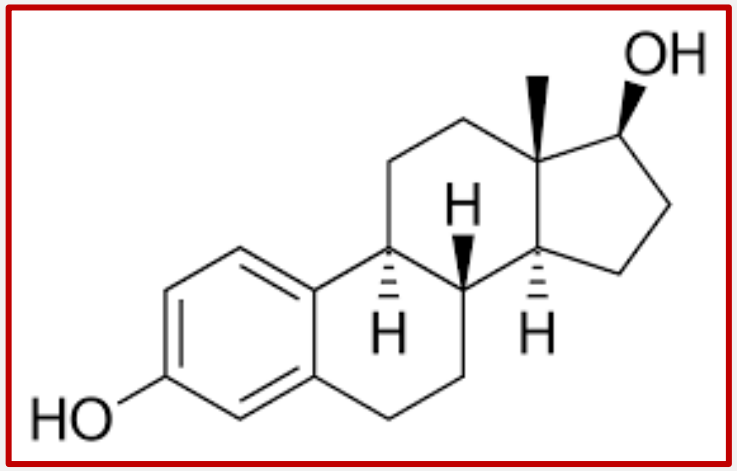
Key Points: Pg BMD

- Pg is important for optimal BMD
- Normal length luteal cycles (12-16 days) are necessary for optimal BMD
- Test, don’t guess; a DUTCH validated cycle-map test provides the most actionable information
- In adolescents, pre and perimenopausal women 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 women, 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

Pg Practice Pointers

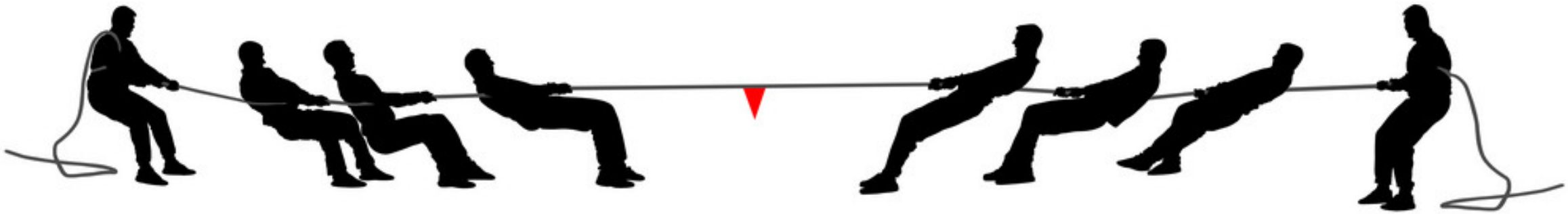
- In premenopausal women with LPDs, including PCOS patients: OMP 300mg days 14-25, or VMP 100-300mg days 14-25 is recommended
- In PMP women with a uterus: OMP 200 or 100mg and VMP 100 or 45mg daily protects the endometrium and may prevent osteoporosis
  - It is unclear whether OMP 100mg provides the same degree of 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 women without a uterus: OMP 200 or 100mg or VMP 100 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

Estradiol (E2)



en.wikipedia.org

Allopathic Medicine vs Function Medicine



what's the opposite of behind the times?

ahead of its time, unconventional, advanced, progressive, avant-garde, pioneering, ground-breaking

depositphotos.com
thesaurus.plus

MHT Guidelines

Menopause: The Journal of The North American Menopause Society
Vol. 24, No. 7, pp. 728-753
DOI: 10.1097/GME.0000000000000921
© 2017 by The North American Menopause Society

POSITION STATEMENT

The 2017 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.

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- **Treatment should be indi… evidence to maximize benefits and minimize risks, with … and risks of continuing or discontinuing [M]HT.**
- **For women aged younge… 10 years of menopause and have no contraindications, the ben… ble for treatment of bothersome VMS and for those at elevated risk for …**

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periodic reevaluation of the benefits and risks of continuing or discontinuing HT.

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MHT Guidelines

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Abstract

The 2017 Hormone Therapy Position Statement of The North American Menopause Society (NAMS) updates the 2012 Hormone Therapy Position Statement of The North American Menopause Society and identifies future research

- 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 women, especially in older women, 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.

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?

Menopausal Hormone E2 Therapy

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Potential Benefits

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How do we optimize these?

E2 Benefits: VMS and VVA

- For most women, all FDA-approved TD E2 products, patches and gels, improve VMS and VVA with serum or DUTCH validated dried urine levels just outside the PMP range
  - TD E2 patch doses as low as 0.025mg/d improve clinical outcomes in most women; serum 20-40pg/mL or DUTCH 0.7-1.8ng/mg
  - TD E2 gel doses are product specific; serum 20-40pg/mL or DUTCH 0.7-1.8ng/mg improve clinical outcomes
    - EstroGel 0.375mg/d is the lowest dose at 4-weeks to improve VMS and VVA
    - Divigel 0.25mg/d is the lowest dose at 4-weeks to improve VVA only, whereas, Divigel 0.50mg/d is the lowest dose at 4-weeks to improve both VMS and VVA

E2 Benefits: Bone Mineral Density

- All FDA-approved TD E2 patches improve BMD and prevent osteoporosis with serum or validated dried urine levels just outside the PMP range
  - TD E2 0.025mg/d patch with serum levels at 20-40pg/mL or DUTCH levels at 0.7-1.8ng/mg
- FDA-approved TD E2 gel products are NOT approved for osteoporosis prevention
  - 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

E2 Benefits: Bone Mineral Density

- All FDA-approved TD E2 patches improve BMD with serum or validated dried urine levels just outside the PMP range

Clinical Pearls: A TD E2 0.025mg/d patch, which improves VMS, VVA, and improves BMD, is a reasonable starting dose when initiating MHT.

Key Points: VMS, VVA, BMD

- For most women, a TD E2 0.025mg/d patch improves VMS, VVA, and BMD at serum or validated dried urine levels just outside the PMP range (serum = 20-40pg/mL, DUTCH = 0.7-1.8ng/mg)
- TD E2 gels are a reasonable alternative for improving VMS and VVA at serum or validated dried urine levels just outside the PMP range (serum = 20-40pg/mL, DUTCH = 0.7-1.8ng/mg)
- TD E2 gels are NOT approved for osteoporosis prevention
- There are no outcome studies using compounded creams
- TD E2 0.025mg/d patch + OMP 200 or 100mg or VMP 100 or 45mg improves clinical outcomes and protects the endometrium

Menopausal Hormone E2 Therapy

E2 Benefits

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

Potential Benefits

- Cognitive Decline

How do we optimize these?

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.

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 woman, 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 woman, no previous MHT ○ Neutral effect on BC incidence and BC mortality • Older PMP woman, 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 women 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 women 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 • Women 50-59 years old had the greatest mortality reduction • With E2 BC mortality 1 in 20 women, 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 women 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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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

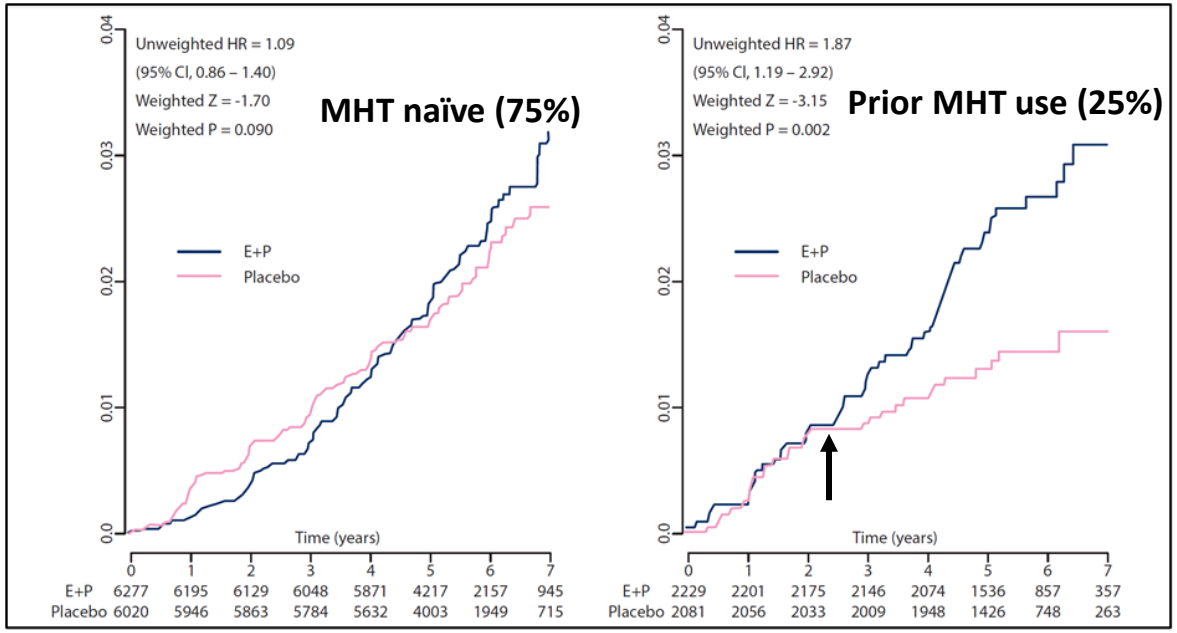
WHI: Data Misinterpretation

- "…[A]ny association that may exist between [M]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% women 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 treatment arm vs placebo: falsely reported higher BC incidence, when actually 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.

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 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

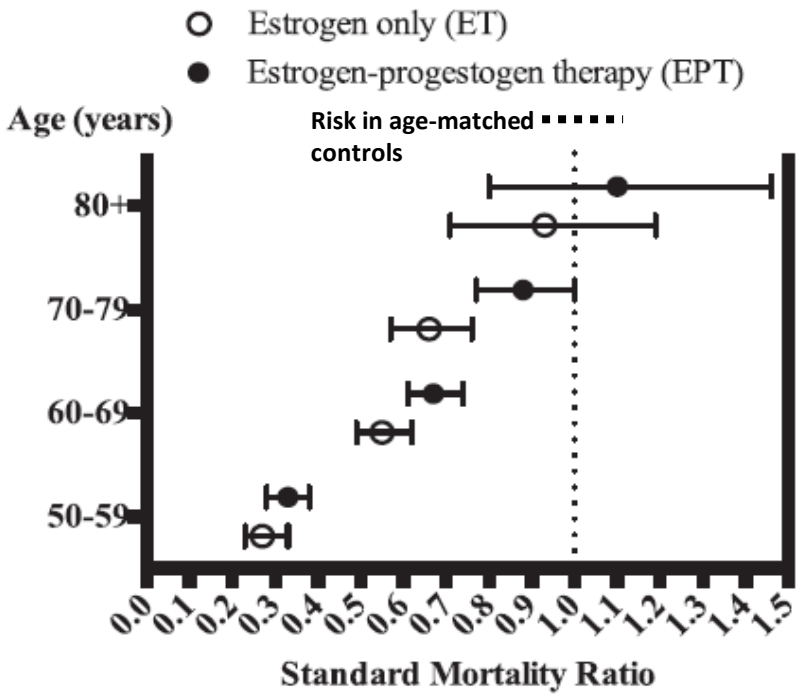
Adapted from Hodis HN, et al. Climacteric. 2018; 21(6): 521-528.

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

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 women 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
    - Women 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
- Conclusion: O-E2, TD E2 patches, and TD E2 gels SS decreased BC mortality up to 54%
  - Even when MHT use was > 10 years
  - Largest mortality reduction was at 5-10 years, in women 50-59, and in those using E2-alone
  - Age at initiation not related to BC mortality
  - **Whereas 1:10 women 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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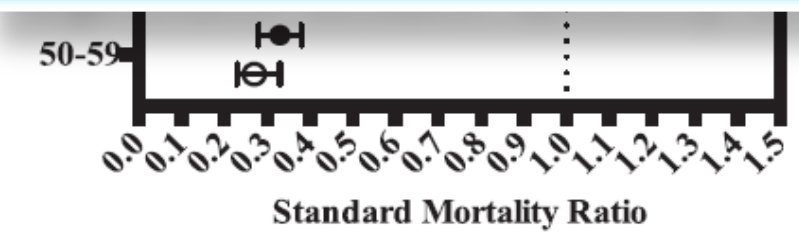
- Study: 15-year observational study using the Finnish Database
  - 489,105 PMP women mean age 52 years, mean MHT exposure: 6.8 ± 6.0 years

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.



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

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 women 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 women 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
- A TD E2 0.025mg/d patch or TD E2 gel decreases BC incidence and mortality

Menopausal Hormone E2 Therapy

E2 Benefits

- Vasomotor Symptoms (VMS)
- Vulvovaginal Atrophy (VVA)
- Bone Mineral Density
- Breast cancer
- **CVD**

Potential Benefits

- Cognitive Decline

How do we optimize these?

Estradiol is Important For CV Health

- Aging and the immune system
  - Aging is associated with a chronic inflammatory state characterized by:
    - Increased proinflammatory cytokines: TNF-α, IL-6, and IL-1β
    - Increased free radical production and decreased redox potential
- 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

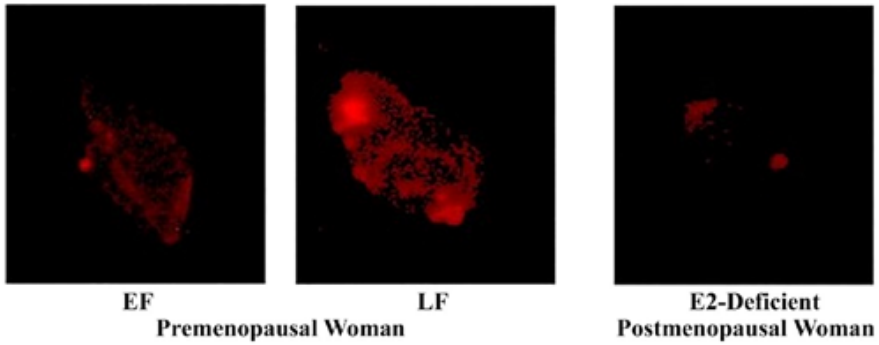
Gubbels Bupp MR. Cellular Immunol. 2015; 294(2): 102-110.
Gubbels Bupp MR, et al. Front Immunol. 2018; 9: 1269.
Mauvais-Jarvis F, et al. Endocrinology. 2020; 161(9): bqaa127.

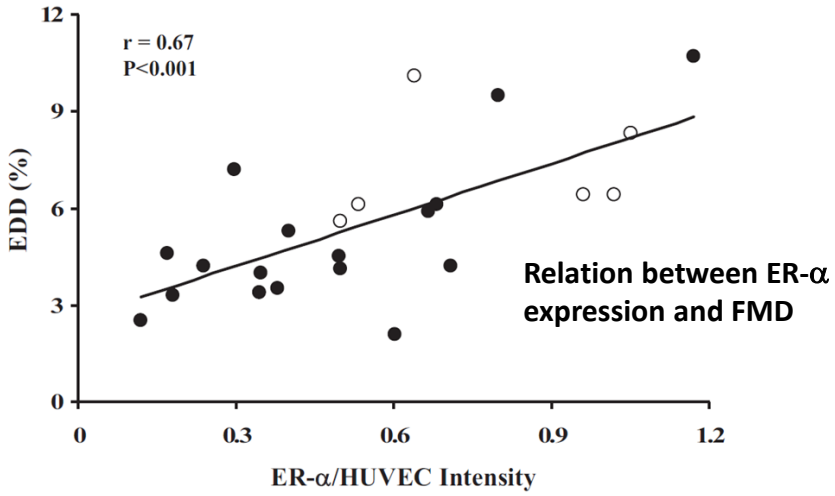
Estradiol and the Endothelium

- 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.

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





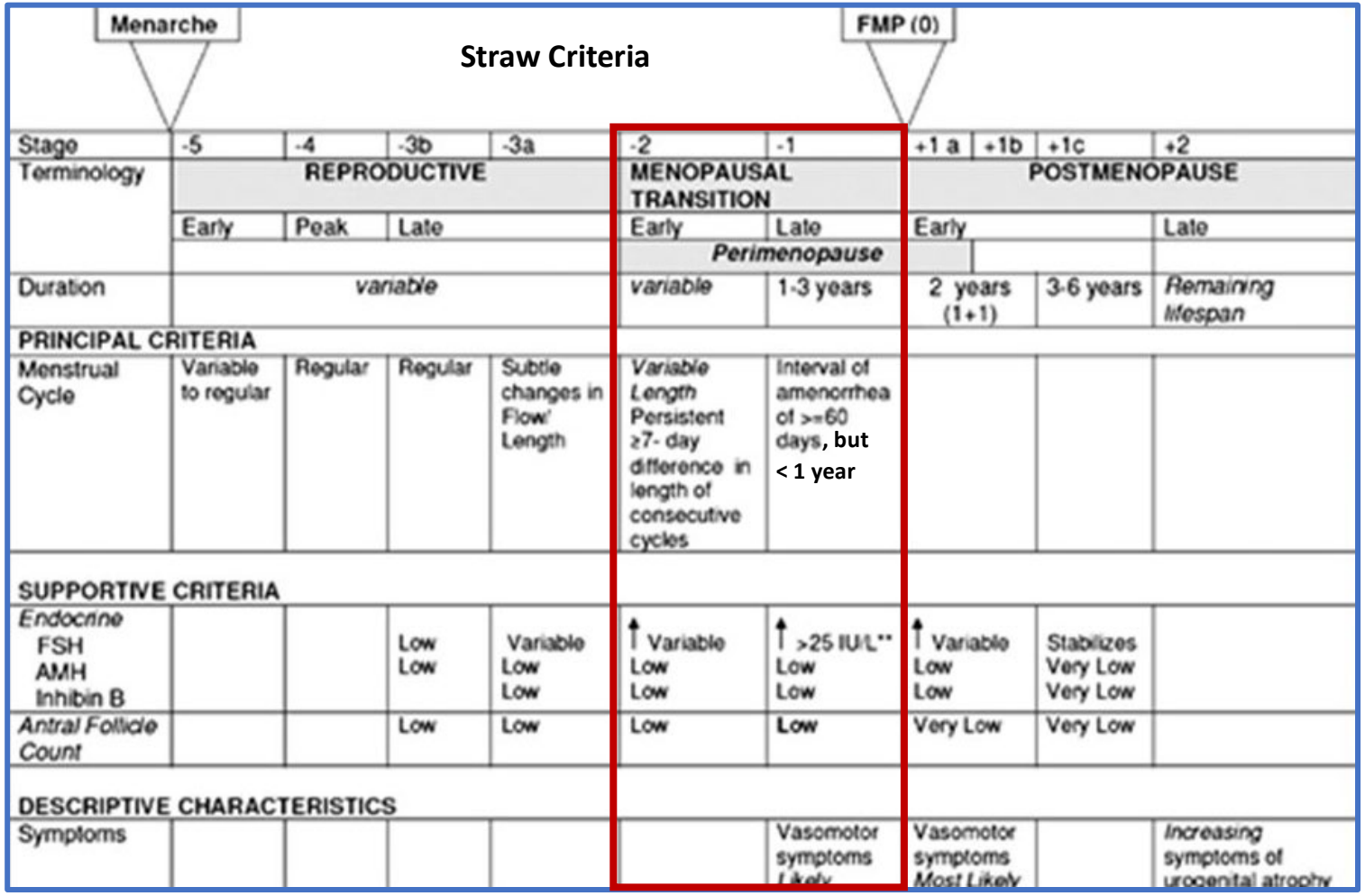
Relation between ER-α expression and FMD

- 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 women 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 women
    - 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.

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

The Menopause Transition: an Overlooked Target



Straw Criteria

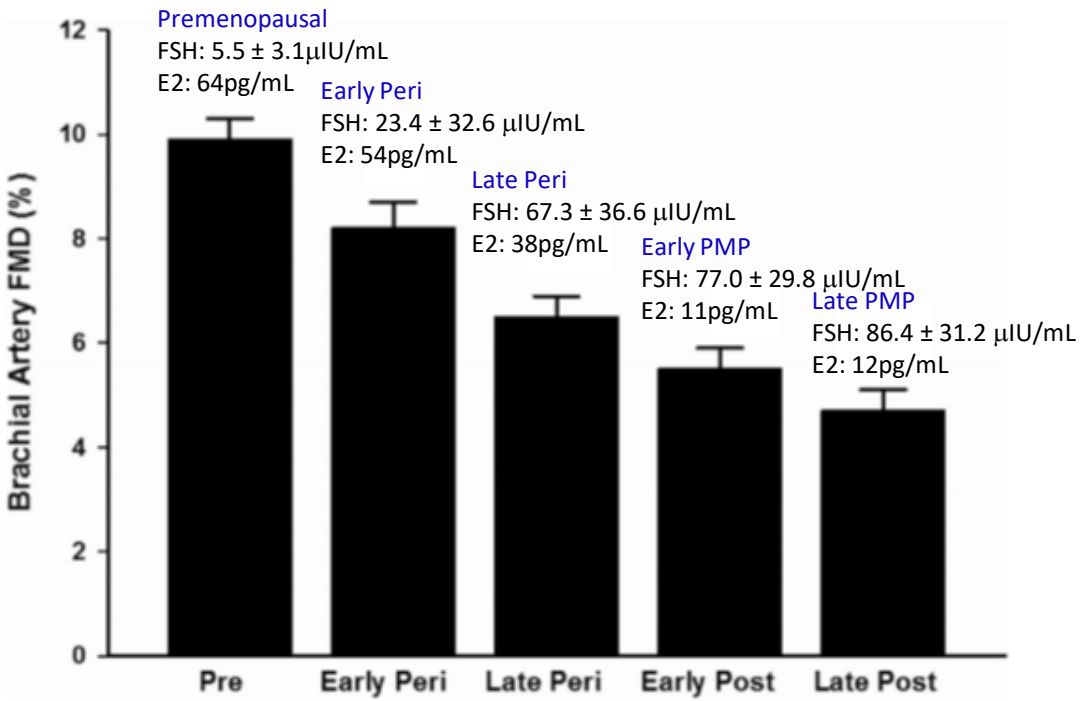
	Menarche					FMP (0)				
Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*variable*				*variable*	1-3 years	2 years (1+1)		3-6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	*Variable Length* Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of >=60 days, **but < 1 year**				
SUPPORTIVE CRITERIA										
Endocrine										
FSH			Low	Variable	↑ Variable	↑ >25 IU/L**	↑ Variable		Stabilizes	
AMH			Low	Low	Low	Low	Low		Very Low	
Inhibin B				Low	Low	Low	Low		Very Low	
Antral Follicle Count			Low	Low	Low	Low	Very Low		Very Low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

Harlow SD, et al. Menopause. 2012; 19(4): 387-395.

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 (MT) affected endothelial function, as measured by brachial artery flow-mediated vasodilation (FMD)
- Study: OS involving 132 healthy women; 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 MT was associated with endothelial dysfunction, independent of traditional RF
  - When compared to premenopausal women:
    - 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 per women, but was NOT SS different than PMP women
  - PMP women, with prolonged E2 deficiency had the lowest FMD
  - Lower FMD strongly associated with higher FSH and lower E2 levels
- **Conclusion: Menopause transition associated with a significant decline in endothelial function**

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

The Menopause Transition: an Overlooked Target

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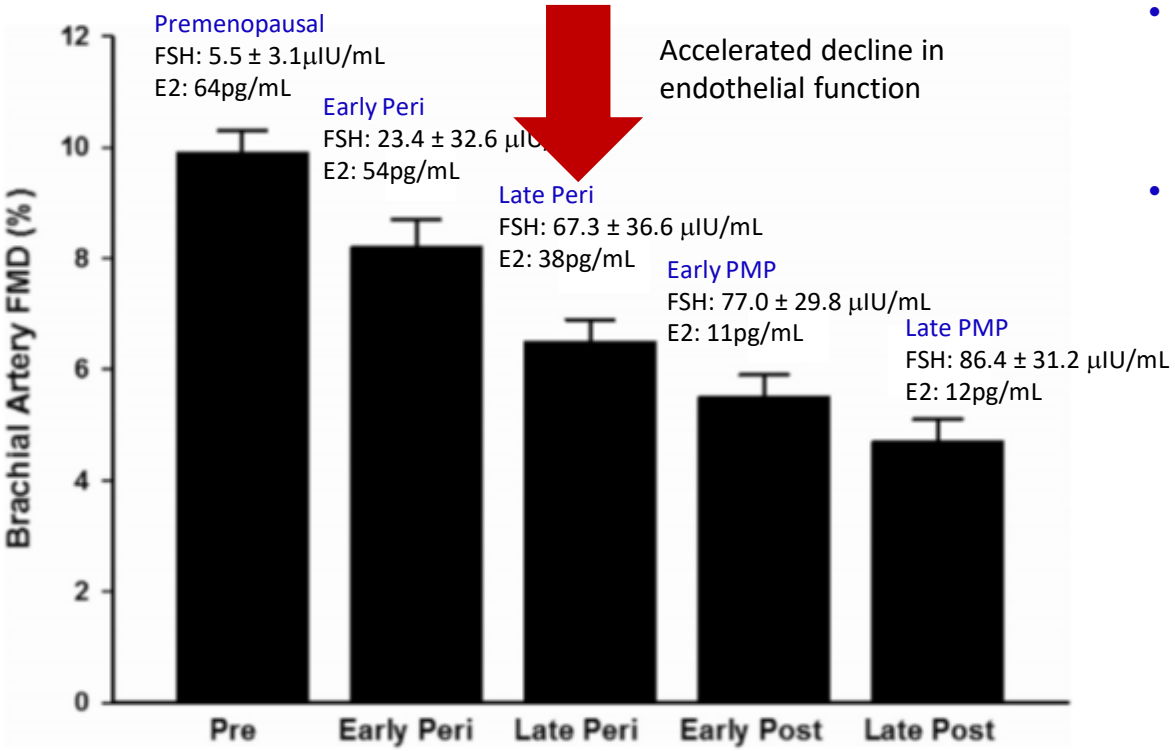

Early peri: 17% decrease vs Late peri: 34% decrease

- Objective: To determine whether the menopause transition affected endothelial function, as measured by brachial artery flow-mediated vasodilation (FMD), a validated prognostic marker for CVD events
- Study: Cross-sectional observational study involving 132 healthy women; 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
- Results:
  - The menopause transition was associated with endothelial dysfunction, independent of traditional RF
  - When compared to premenopausal women
    - FMD was SS lower in early peri ($P = 0.03$) late peri ($P < 0.001$), and early and late PMP ($P < 0.001$)
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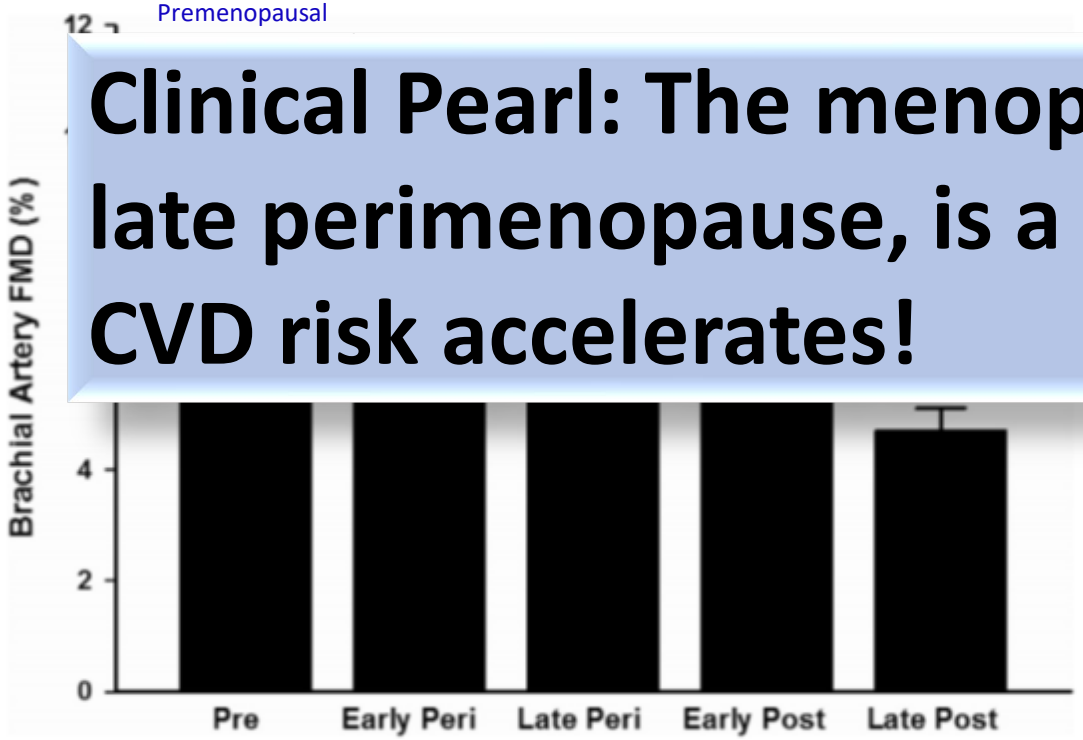

Early peri: 17% decrease vs Late peri: 34% decrease

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

- Objective: To determine whether the menopause transition affected endothelial function, as measured by brachial artery flow-mediated vasodilation (FMD), a validated prognostic marker for CVD events
  - When compared to premenopausal women
    - FMD was SS lower in early peri (P = 0.03) late peri (P < 0.001), and early and late PMP (P < 0.001)
  - Late perimenopause associated with SS lower FMD than either pre- or early perimenopausal women, but was NOT SS different than PMP women
    - Early vs late perimenopause: 17% vs 35% FMD reduction
  - PMP women, with prolonged E2 deficiency had the lowest FMD
  - Lower FMD associated with higher FSH and lower ovarian hormone levels
- **Conclusion: Menopause transition associated with a significant decline in endothelial function**

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

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

Yes!

E2, the “Timing Hypothesis," and CVD Risk

Studies	Study Drugs/Doses	Results
Studies documenting mixed results		
WHI	• CEE-alone (0.625mg/d) • Placebo	• PMP women age 50-59: 40% decreased MI risk and all-cause mortality • PMP women age 60-69: neutral effects on CV outcomes • PMP women 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 women 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 women 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 women 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 woman was prescribed and used an E2-based MHT, the greater the risk reduction • All risk reductions were comparable in PMP women initiating E2 < age 60 and in women initiating therapy ≥ 60 years or older

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Key Points: E2 and CVD Risk

- Premature menopause and early surgical menopause are associated with increased CVD risk
- Estradiol decreases CV morbidity and mortality
  - 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 women as early as possible, okay to initiate therapy later, and treatment may be continued for > 10 years, as long as 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

Key Points: E2 and CVD Risk

- Estradiol decreases CV morbidity and mortality
  - Recently menopausal women, depending on CVD risk (those with subclinical ASCVD), may require higher serum 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 women or women further from menopause onset probably do best with serum E2 levels just outside the PMP range (20 to < 40pg/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 women

Key Points: E2 and CVD Risk

- Estradiol decreases CV morbidity and mortality

Clinical Pearls: 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 women

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?

E2 and Cognition: Mixed and Confusing Data

- Some studies document positive effects, some documenting no benefit, while others document harm
- Mixed results may be secondary to:
  - Different demographic study populations to include genetics,
  - Different formulations and doses used,
  - Different endpoints tested using different methodologies, and
  - Different study durations
- Most studies were too short to discern E2's protective effects
- Most studies were not designed to measure cognitive performance or AD risk as a primary endpoint

E2: The Plausibility Argument For Cognitive Benefits

- E2 has a significant role in overall brain health and cognitive function
  - E2 increases CNS antioxidants, decreases free radicals, and mitochondrial damage
  - E2 improves cerebral metabolic flow and rate
  - E2 regulates glucose and oxidative metabolism, mitochondrial function and promotes ATP generation; E2 is involved in DNA repair, attention and memory processes
  - Enhances synaptic plasticity, neurite growth, hippocampal neurogenesis, and protects against neural injury and apoptosis

Fischer B, et al. Fertil Steril. 2014; 101(4): 898-904.
L'Hermite M, et al. Climacteric. 2017; 20(4): 331-338.
Russell JK, et al. Neurotherapeutics. 2019; 16(3): 649-655
Petresi S, et al. Post Reprod Health. 2019; 25(4): 200-206.

E2: The Plausibility Argument For Cognitive Benefits

- Cognitive changes during the late perimenopause and during menopause are very common
  - Brain fog and decreased attention, processing speed, and memory, which manifest as: difficulty focusing and forgetfulness
- Cognitive changes are related to changing E2 levels and ER expression
  - ER-α and ER-β expression important for executive functioning, attention, and memory processes
- Higher estrone (E1) levels associated with poorer cognition, specifically working memory performance – a strong argument for TD E2
  - Oral E2: first-pass metabolism with high E1 to E2 ratio vs TD E2 with its physiologic 1:1 E2: E1 ratio

Fischer B, et al. Fertil Steril. 2014; 101(4): 898-904.
L'Hermite M, et al. Climacteric. 2017; 20(4): 331-338.
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Table 1. The effects of estrogen on general brain health, cognition and dementia.

Effect of estrogen on the brain	Effect of estrogen on cognition	Effect of estrogen on dementia
• Improves **synapse formation** on dendritic spines in hippocampi and increases **choline acetyltransferase activity** in the basal forebrains as well as hippocampi of rats.[21,26] • Estrogen **increases glucose transport across the blood–brain barrier** and improves glucose utilization in the brain, and thus prevents the neuroglucopenia-induced cascade of immediate and delayed reactions leading to neuronal degeneration.[21] • Contributes to cellular **maintenance and survival of neurons** via modulation of the neurotrophins and encourages neuron functioning due to its anti-apoptotic effects.[25] • Has neuroprotective effects such as **inhibition of Aβ formation**, stimulation of cholinergic activity and **reduction of oxidative cell damage**. Estrogen also prevents Aβ-amyloid from inducing a rise in intracellular calcium and from causing mitochondrial damage.[39–41]	• Modulates the structure and function of the hippocampus and in turn shown to improve **object recognition and object location performance.**[55] • Improves pre-frontal lobe-dependant **executive functioning**in women and also in middle-aged ovariectomised monkeys.[56] • Modulates performance on **verbal memory and fluency**. Differences in verbal fluency performance can be seen across the menstrual cycle, with high estrogens associated with better performance.[57] • Estrogen therapy increased prefrontal cortex blood oxygenation levels during tests of **verbal and spatial working memory**, and this increase was associated with fewer errors (double-blind trial).[58,59] • Rodent studies which illustrate that estrogen-induced rapid membrane-signalling enhances social behaviour.[60,61]	• Prevents the hyper-phosphorylation of the tau protein, in turn causing a **decreased formation of neurofibrillary tangles;** the insoluble neurotoxic protein believed to be one of the key players of AD pathology.[61] • **Post-mortem brain samples from female AD patients show greater reduction of estrogen** levels in AD brains relative to controls, suggesting that brain estrogen deficiency is associated with AD pathology.[63] • Administration of hormone replacement therapy for 2–3 years in the early menopausal years (before 65) has been shown to **decrease the risk of cognitive impairment.**[64] • WHISCA drug trial found a **significant increase in the risk of dementia/mild cognitive impairment late menopausal women** due to estrogen interventions (support for the 'critical window' hypothesis).[65,66]

Petresi S, et al. Post Reprod Health. 2019; 25(4): 200-206.

E2: The Plausibility Argument For Cognitive Benefits

Does MHT (TD E2 + OMP or VMP) improve cognitive performance and prevent Alzheimer's Disease?

E2 and Cognition

Cognition Studies Summarized		
Studies	Study Drugs/Doses	Results
Studies documenting increased cognitive impairment		
WHIMS	• CEE 0.625mg/d alone • CEE 0.625mg/d + continuous MPA 2.5mg/d • Placebo	• Significant increase in cognitive impairment in PMP women > 65 years old • CEE alone –non-SS increase in cognitive impairment
Studies documenting no benefit and no harm: Critical Window Hypothesis		
WHIMS-Y	• CEE 0.625mg/d + continuous MPA 2.5mg/d • Placebo	• In younger PMP (treated 50-55 years old) women who initiate therapy soon after menopause, MHT is neither beneficial nor harmful
KEEPS-Cog	• PREMARIN 0.45mg/d + PROMETRIUM 200mg/d x 12d • CLIMARA 0.05mg/d + PROMETRIUM 200mg/d x 12d • Placebo	• Neither cognitive benefit, nor harm for either MHT group • TD E2 patch decreased amyloid-β deposition, particularly in apolipoprotein e4 (APOE e4) carriers
KEEPS-Cog substudy	• PREMARIN 0.45mg/d + PROMETRIUM 200mg/d x 12d • CLIMARA 0.05mg/d + PROMETRIUM 200mg/d x 12d • Placebo	• Study suggests that cognitive function is not only affected by hormones, but is affected by other factors including sleep, HPA axis resiliency, and inflammation • The TD E2 (Climara 0.05mg/d) patch treated women with improved sleep quality had less amyloid-β deposition on PET scanning when compared to placebo • In both MHT groups (CEE 0.45mg/d, CLIMARA 0.05mg/d) better global sleep quality was associated with higher visual-attention and executive functions • APOE e4 status did not impact results
ELITE-Cog	• O-E2 1mg/d • O-E2 1mg/d + VMP GEL 45mg/d, days 1-10 (brand name unknown) • Placebo	• Irrespective of when o-E2 was initiated, o-E2 did not affect verbal memory, executive function, or global cognition
Yaffe	• MENOSTAR 0.014mg/d patch • Placebo	• In older PMP women, the TD E2 patch did not improve cognitive performance over a 2-year timeframe compared to placebo
Studies documenting cognitive benefit		
Cache County	• Unknown drugs, doses, routes of administration (2013, 2019 publications)	• MHT use for long durations was positively associated with cognitive status • Older women had a greater benefit when compared with younger women • The later the onset of menopause, and the longer a PMP woman uses MHT, the greater the association with higher cognitive status later in life (especially true for older women)
Asthana (2 separate studies)	• Study 1 (1996): ESTRADERM 0.05mg/d vs Placebo • Study 2 (2001): ESTRADERM 0.1mg/d vs Placebo • Small pilot studies	• Both studies: PMP women had mild-moderate cognitive impairment • ESTRADERM 0.05mg/d: Significantly improved attention and verbal memory compared to placebo • ESTRADERM 0.1mg/d: Significantly improved semantic, verbal, and visual memory compared to placebo
Joffe	• CLIMARA 0.05mg/d • Placebo	• Otherwise, healthy, symptomatic, peri and PMP women without cognitive impairment • Significantly improved executive functioning when compared to placebo

E/E2, May Increase Cognitive Decline

- Women's Health Initiative Memory Studies (WHIMS)
  - 7479 PMP women > 65 years old
  - Result: CEE + MPA vs placebo (4-year) and CEE-alone vs placebo (5-year)
    - 4532 PMP women, CEE + MPA: Doubled the dementia incidence when compared to placebo; suggested hastened already existing neuropathology
    - 2947 PMP women, CEE-alone: 49% increase
- Finnish OS study: 0-E2, TD E2 + progestins
  - Case control comparison evaluating whether MHT had an effect on AD risk and whether risk associated with treatment age at initiation or duration
  - 84,739 PMP women with AD vs age matched controls
  - Results: 9-17% increased AD risk; age at initiation and treatment < 10 years not a determinant of AD risk, but treatment > 10 years was a risk; risk same for E2 + progestin and E2-alone

E/E2, May Increase Cognitive Decline

- Women's Health Initiative Memory Studies (WHIMS)
  - 7479 PMP women > 65 years old
  - Result: CEE + MPA vs placebo (4-year) and CEE-alone vs placebo (5-year)

Clinical Pearl: Both studies used progestins, which have been shown to decrease cognitive performance, suggesting these studies are not relevant to clinical practice.

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  - Results: 9-17% increased AD risk; age at initiation and treatment < 10 years not a determinant of AD risk, but treatment > 10 years was a risk; risk same for E2 + progestin and E2-alone

E2, “Critical Window Hypothesis,” and Cognition

The “critical window hypothesis” states that MHT can have a positive impact on cognition in peri-menopausal and PMP women when initiated early and continued up until the age of 60 years old when dementia risk is small, but might have a negative effect on cognition in PMP > 60 years old

E2, “Critical Window Hypothesis,” and Cognition

- WHIMS-Young: Does MHT initiated early after menopause influence cognition years later?
  - 1326 PMP women 50-55 years old when started MHT (CEE-alone or CEE + MPA)
  - Cognitive tests performed at age 67.2, which was 7.2 years after MHT discontinuation and 14.2 years after randomization
  - Results: In younger PMP women who initiate MHT soon after menopause, MHT is neither beneficial or harmful

E2, “Critical Window Hypothesis,” and Cognition; No Benefit, No Harm

- KEEPS-Cog: A 4-year cardiovascular study
  - 727 PMP women, within 3-years of menopause randomized to TD E2 0.05mg/d patch or CEE 0.45mg/d + OMP 200mg x 12-days
  - Results: Compared to placebo, there was neither cognitive benefit, nor harm; TD E2 resulted in less amyloid-β deposition, particularly in APOE ε4 PMP women
- ELITE-Cog: A 5-year cardiovascular study
  - 643 PMP woman stratified as early PMP (< 6 years) or late PMP (> 10 years) to 1mg oral E2 + VMP 45mg x 10 days vs placebo
  - Results: Compared to placebo, o-E2 did not affect verbal memory, executive functions, or global cognition, irrespective of timing; including women > 10 years PMP; neither cognitive benefit, nor harm

E2, “Critical Window Hypothesis,” and Cognition; No Benefit, No Harm

- KEEPS-Cog: A 4-year cardiovascular study
  - 727 PMP women, within 3-years of menopause randomized to TD E2

Clinical Pearl: Though micronized progesterone was used in both studies, neither study was long enough to really assess AD risk

  - 643 PMP woman stratified as early PMP (< 6 years) or late PMP (> 10 years) to 1mg oral E2 + VMP 45mg x 10 days vs placebo
  - Results: Compared to placebo, o-E2 did not affect verbal memory, executive functions, or global cognition, irrespective of timing; including women > 10 years PMP; neither cognitive benefit, nor harm

E2, May Improve Cognitive Performance

- Asthana (1999, 2001): 3-month RCT pilot (8 treatment weeks)
  - 1999 Study: 12 PMP women 66-89 years old, baseline E2: 15pg/mL; TD E2 0.05mg/d patch vs placebo; treatment E2: 55-100pg/mL
    - Results: Treatment group with SS improvement in attention and verbal memory, with a trend towards increased visual memory
  - 2001 Study: 20 PMP women 61-90 years old, baseline E2: 15pg/mL; TD E2 0.1mg/d patch vs placebo; treatment E2: 70-200pg/mL
    - Results: high-dose patch SS improved semantic, verbal, and visual memory
- Cognitive benefits decreased when treatment was terminated and E2 levels returned to baseline

E2, May Improve Cognitive Performance

- Joffe: (2006) 3-month RCT, which cognitive domains E2 influences
  - Study: 52 peri- or PMP women, 40-60 years old; TD E2 0.05mg patch; baseline E2 19-42pg/mL; no on treatment E2 serum results
  - Results: The TD E2 patch improved executive functioning
- Cache County OS: (2013, 2019) ongoing longitudinal study assessing reproductive E/E2's lifetime exposure on cognitive function and AD
  - 2013: in PMP women, if MHT started within 5-years and continued for > 10 years, ~ 37% decreased AD risk
  - 2019: older women had > benefit that younger women (longer use); the longer a woman used MHT the > benefit; timing SS associated with 3MS exam, initiation within 5-years high scores than if initiated ≥ 6 years

E2, May Improve Cognitive Performance

- Joffe: (2006) 3-month RCT, which cognitive domains E2 influences
  - Study: 52 peri- or PMP women, 40-60 years old; TD E2 0.05mg patch; baseline

Clinical Pearls: Estradiol is NOT indicated to improve cognitive performance, counsel patients that it may or may not improve cognition, set expectations.

  - 2013: in PMP women, if MHT started within 5-years and continued for > 10 years, ~ 37% decreased AD risk
  - 2019: older women had > benefit that younger women (longer use); the longer a woman used MHT the > benefit; timing SS associated with 3MS exam, initiation within 5-years high scores than if initiated ≥ 6 years

Does MHT (TD E2 + OMP or VMP) improve cognitive performance and prevent Alzheimer's Disease?

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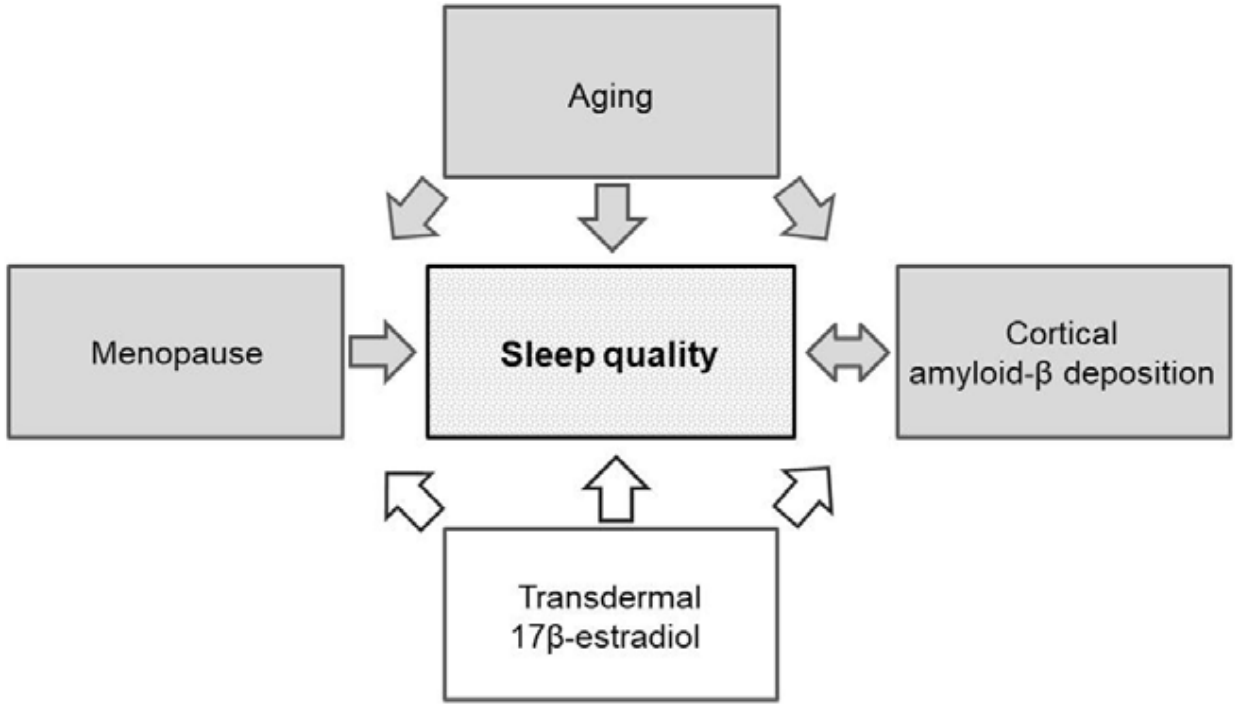
E2, Cognition, and Inflammatory Triggers

Sleep quality and cortical amyloid-β deposition in postmenopausal women of the Kronos early estrogen prevention study

Burcu Zeydan[a,b], Val J. Lowe[a], Nirubol Tosakulwong[c], Timothy G. Lesnick[c], Matthew L. Senjem[a,d], Clifford R. Jack, Jr.[a], Julie A. Fields[e], Taryn T. James[f,g], Carey E. Gleason[f,h], N. Maritza Dowling[i], Virginia M. Miller[j,k] and Kejal Kantarci[a]



- Gray arrows: potential risks
- White arrows: potential benefits

- Objective: Assess the associations between self-reported sleep quality with cortical amyloid-β and cognitive function in women on MHT vs placebo 3-years after completion of study drugs
- Study: KEEPS RCT with 72 participants; mean age ~ 60; TD E2 0.05mg/d patch or CEE 0.45mg/d + OMP 200mg x 12 days
- Results:
  - In the TD E2 group: those with improved sleep quality had less amyloid-β on PET scanning; mean serum E2: 44pg/mL
  - Both treatment arms: better sleep associated with improved visual attention and executive function
  - APO E ε4 did not significancy impact results
- **Conclusion: MHT, especially TD E2, may influence the effects of sleep on cognitive performance and amyloid-β accumulation and clearance**

Zeydan B, et al. Neuroreport. 2021; 32(4): 326-331.

E2, Cognition, and Inflammatory Triggers

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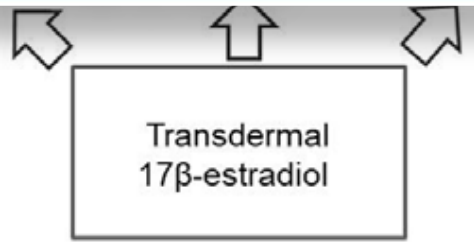
- Objective: Assess the associations between self-reported sleep quality with cortical amyloid-β and cognitive function in women on MHT vs placebo 3-years after completion of

Clinical Pearl: Study suggests that cognitive function is affected not only by hormones but by other factors, to include sleep quality, HPA axis resiliency, and inflammation



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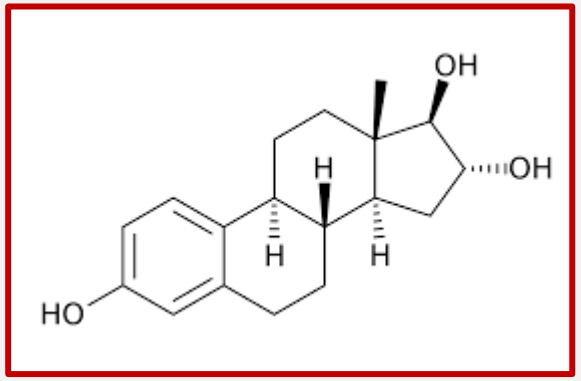
Key Points: E2 and Cognition

- TD E2 should not be prescribed to improve cognitive performance
- Most studies were too short to assess MHT and AD risk
- A TD E2 0.025mg/d patch has not been assessed regarding cognitive performance, a 0.05mg/d patch and 0.1mg/d patch improved cognitive performance in older PMP women with mild-moderate AD (very small studies)
- The Cache County OS study is the most promising, stating: MHT, when initiated within 5-years of menopause and continued for > 10 years may reduce AD risk

E2 Practice Points

- Initiate MHT as close to menopause as possible, continue as long as appropriate with ongoing risk stratification, surveillance, and FU testing
- A TD E2 0.025mg/d patch + OMP 200 or 100mg or VMP 100 or 45mg
  - Protects the endometrium
  - Improves VMS, VVA, and BMD
  - Decreases BC mortality
  - Improves cardiovascular outcomes, and
  - May or may not improve cognitive performance
- For those PMP women, who cannot tolerate a patch, TD E2 gel products are reasonable options, however, not FDA-approved for BMD
- Compounded products probably work, but have no outcome data
- Test, don't guess, include metabolomics, which are necessary for a successful hormone practice

Estriol (E3)



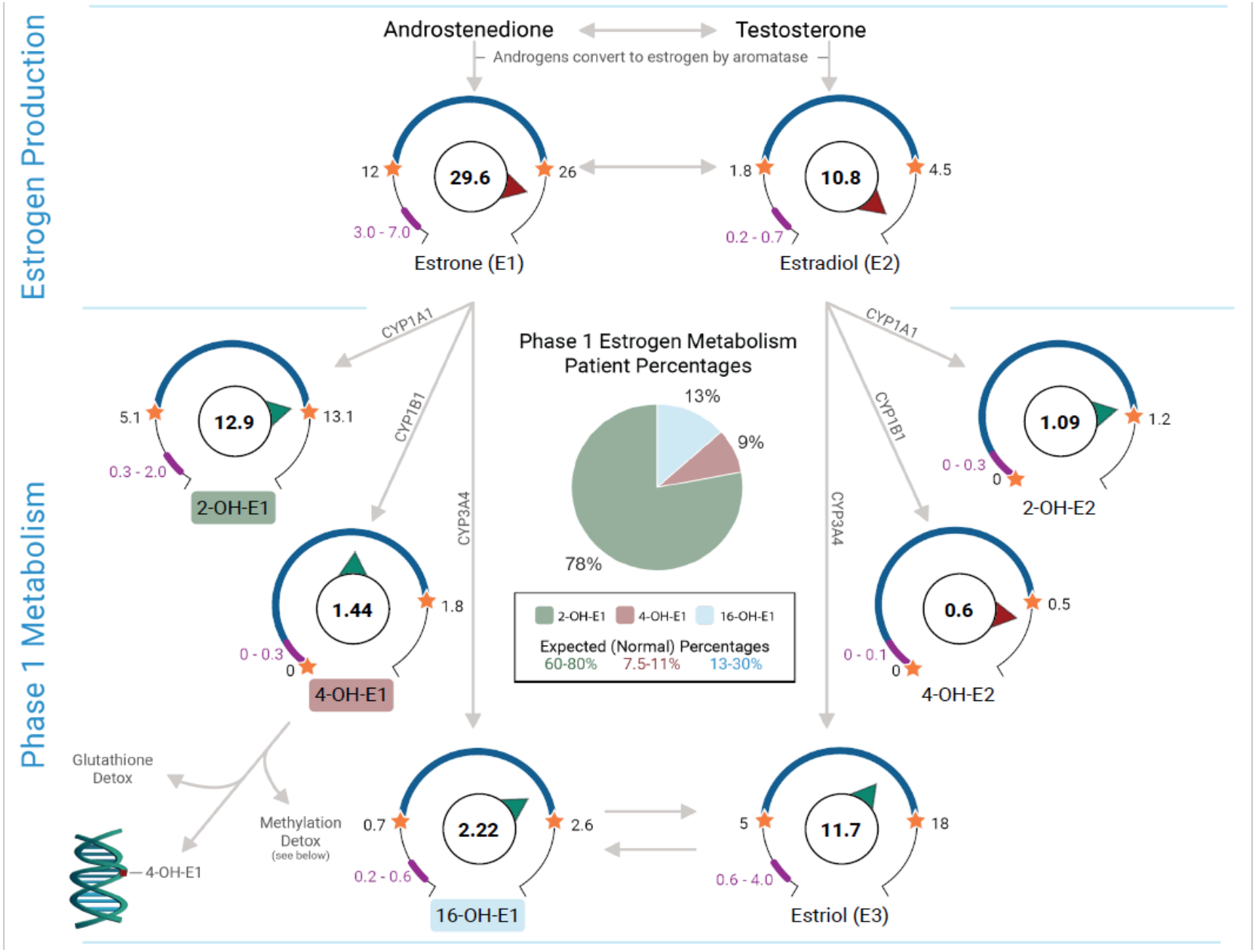
en.wikipedia.org

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.

Estrogen Metabolism



E3 (E3): Clinical Utility

- Menopause
  - 40-50% of PMP women 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.

E3 (E3): Clinical Utility

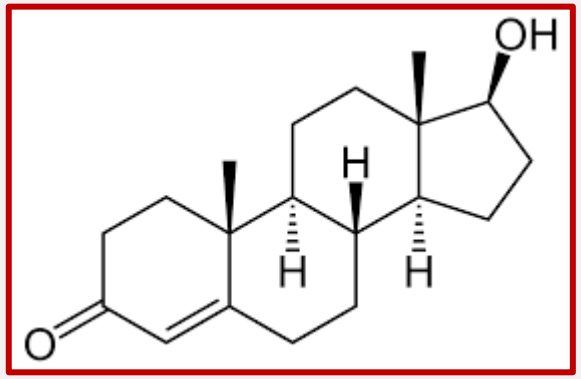
- Immune modulator: Needs more studies
  - May have potent immunomodulatory effects
    - Decreases inflammatory cytokines, i.e. TNF-α, down-regulating NF-$\kappa\beta$, and upregulates anti-inflammatory cytokines, i.e. IL-10
  - Estrogens have an emerging neuromodulatory and neuroprotective role in 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.

E3 Key Points and Practice Pointers

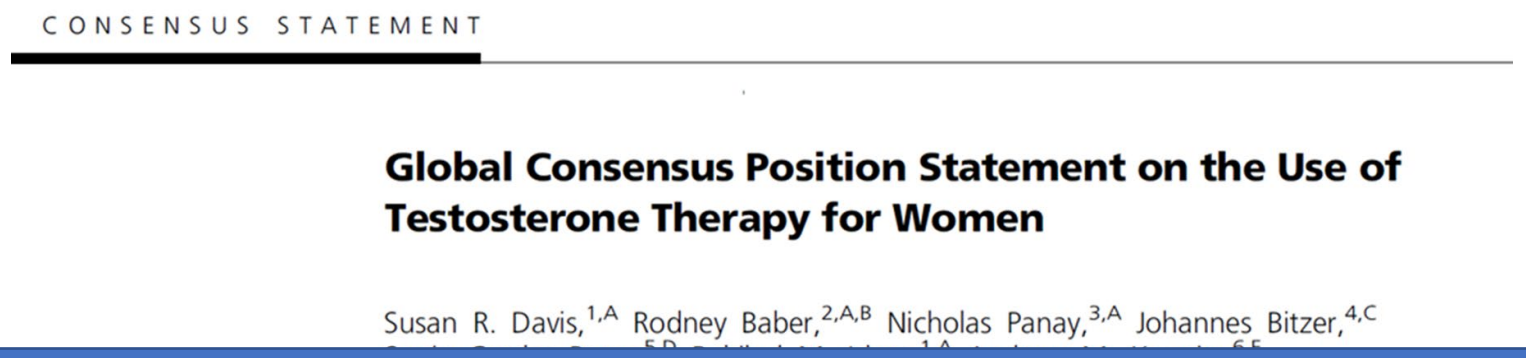
- Estriol must be compounded
- Most support its vaginal use for VVA and maybe VMS
- Potential role in MS (oral or transdermal E3) for both men and women
- No large studies documenting E3's role in breast protection, plausibility argument, since it binds to ER-β, which is antiproliferative
- VE3 dosing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

Testosterone (T)



en.wikipedia.org

TTH in Women: 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 women should be monitored using LC-MS/MS**
- **Measure total testosterone (TT) and SHBG, less data on free T**
- **Uncertain association between T 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.

TTH in Women: The Guidelines

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Susan R. Davis,[1,A] Rodney Baber,[2,A,B] Nicholas Panay,[3,A] Johannes Bitzer,[4,C] Sonia Cerdas Perez,[5,D] Rakibul M. Islam,[1,A] Andrew M. Kaunitz,[6,E] Sheryl A. Kingsberg,[7,F] Irene Lambrinoudaki,[8,G] James Liu,[9,E] Sharon J. Parish,[10,H] JoAnn Pinkerton,[11,F] Janice Rymer,[12,I] James A. Simon,[13,14,H] Linda Vignozzi,[15,16,C] and Margaret E. Wierman[17,J]

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TTH in Women: 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

Sharon J. Parish, MD,[1,2] James A. Simon, MD,[3] Susan R. Davis, MBBS, PhD,[4] Annamaria Giraldi, MD, PhD,[5,6] Irwin Goldstein, MD,[7,8] Sue W. Goldstein, BA, CSE,[8] Noel N. Kim, PhD,[9] Sheryl A. Kingsberg, PhD,[10] Abraham Morgentaler, MD,[11] Rossella E. Nappi, MD, PhD,[12] Kwangsung Park, MD, PhD,[13] Cynthia A. Stuenkel, MD,[14] Abdulmaged M. Traish, PhD,[15] and Linda Vignozzi, MD[16,17]

- **A clinical practice guideline for TTh in women 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**
- **Women make ~ 0.2-0.25mg/d, a healthy woman's mid-luteal TT level ranges from: 15-228ng/dL with a mean ~ 58ng/dL**
- **Dosing should be 1/10th to 1/15th a male dose: Male T gel 50mg: Woman's 3.5-5mg/d should maintain physiologic levels**
- **Serum LC-MS/MS 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.

TTH in Women: The Guidelines

International Society for the Study of Women's Sexual Health
Clinical Practice Guideline for the Use of Systemic
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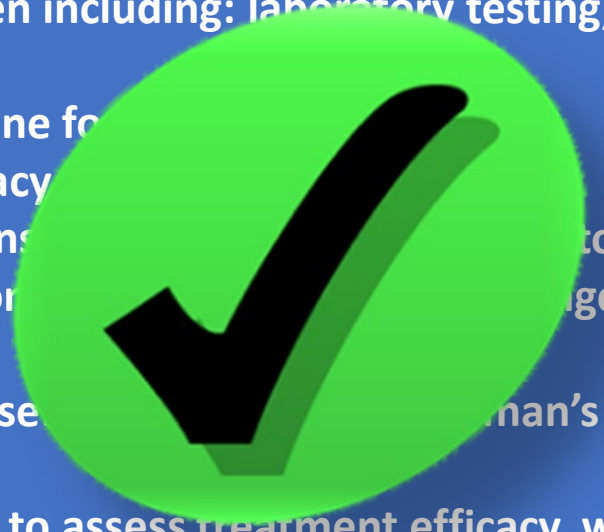

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T Production in Women

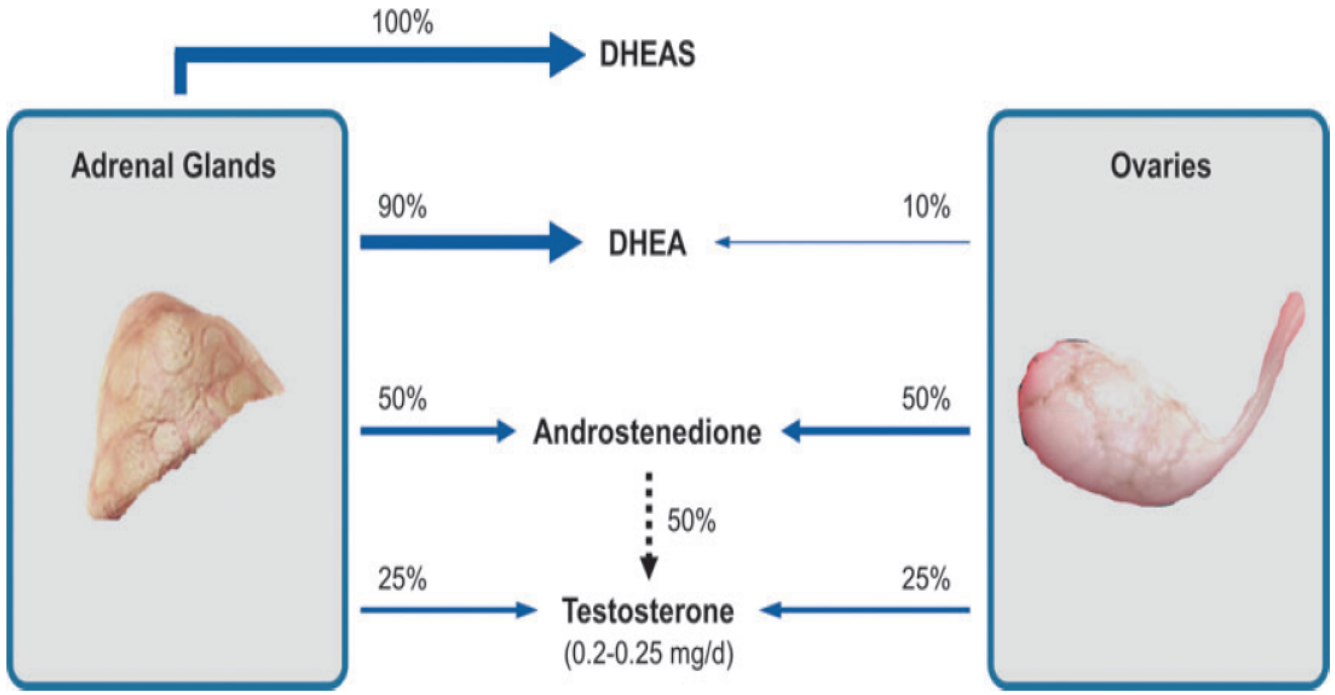


FIG. 1. Relative production of circulating androgens in the adrenal glands and ovaries. The substantial contribution of androstenedione to circulating testosterone is shown by a dashed arrow and involves peripheral tissue conversion. DHEA = dehydroepiandrosterone; DHEA-S = dehydroepiandrosterone sulfate.

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

TTh: What Do We Know?

- There is no FDA-approved T formulation for women
  - Either off-label male formulations or compounded
- T is safe, effective, and does not increase CVD, BC, or endometrial cancer risk
  - Most T studies document that serum total T, FT, bioavailable T levels at the high end of the RR are important for improved clinical success
  - T patch: 0.3mg/d; T gel: ~ 10mg/d or 50mg/week; T cream: ~ 10mg/d; T pellets: 50mg-150mg every 3-4 months
  - Studies that documented clinical success with serum T levels that were somewhat or many times higher than the ULN, found no significant adverse events
- Serum is the gold standard for monitoring TTh
  - Testosterone can be monitored in urine; however, similar to TTh monitoring in men, must be aware of the UGT SNP

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: 50-150mg/3-4 months
- Patients require less T than you think!

Monitoring after 12 treatment weeks

- Blood
- Urine for comprehensiveness

Debunking TTh Myths

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

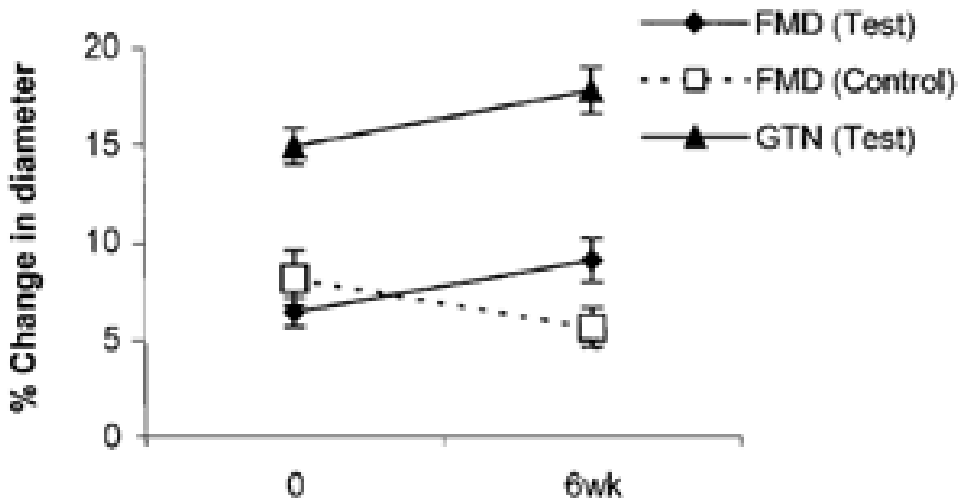
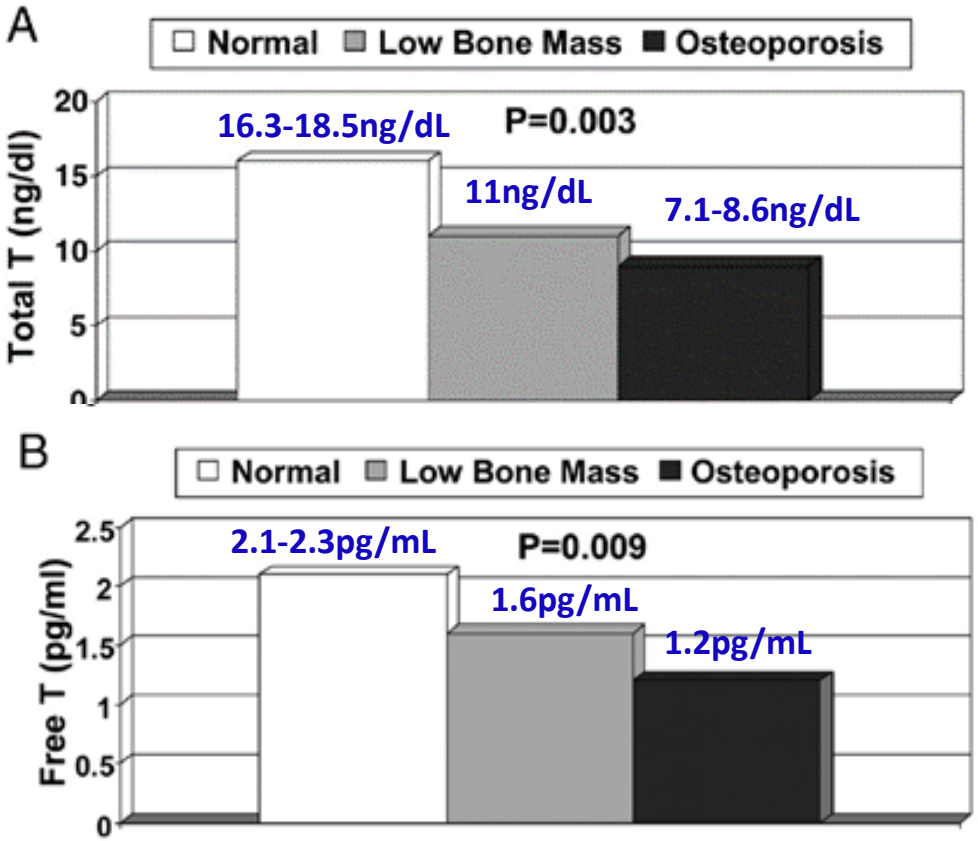


FIG. 1. Mean (±SEM) FMD- and GTN-mediated vasodilation in testosterone-treated women and mean FMD in controls, expressed as percentage change in vessel diameter.

- TTh improves endothelial function in women on stable E2 (2001)
  - First RCT to assess TTh's effect (T pellet 50mg) in women on stable E2 therapy (50mg pellet) for ≥ 6- months; baseline studies pre-treatment and 6-weeks post treatment
  - Results: 33 treated women vs 15 non-MHT users
    - TTh SS improved FMD (42% increase) and smooth muscle vasodilation when compared to PMP women not using MHT
    - T levels SS different from baseline to 6-weeks
      - Baseline: 28.5 ± 2.3ng/dL; 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) dilation, 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.

Higher Endogenous T levels ⇨ Increased BMD



Higher Serum Free Testosterone Concentration in Older Women Is Associated with Greater Bone Mineral Density, Lean Body Mass, and Total Fat Mass: The Cardiovascular Health Study

Chevon M. Rariy, Sarah J. Ratcliffe, Rachel Weinstein, Shalender Bhasin, Marc R. Blackman, Jane A. Cauley, John Robbins, Joseph M. Zmuda, Tamara B. Harris, and Anne R. Cappola

- Study: Community-dwelling observational study looking at the association between endogenous T levels and BMD
- Results: 232 women older than 65 years old were included, 18% on E
  - Overall, there was a step-wise increase in BMD with increasing total T and free T levels
  - Higher total T levels were significantly associated with increased hip and lumbar BMD, regardless of E2 level
  - Higher free T levels were significantly associated with increased hip BMD, only with increased E levels
  - Free T was significantly associated with increased fat mass
- **Conclusion: Total T plays a significant role in maintaining BMD in older women who have low E2 levels; Higher circulating T levels are associated with increased BMD**

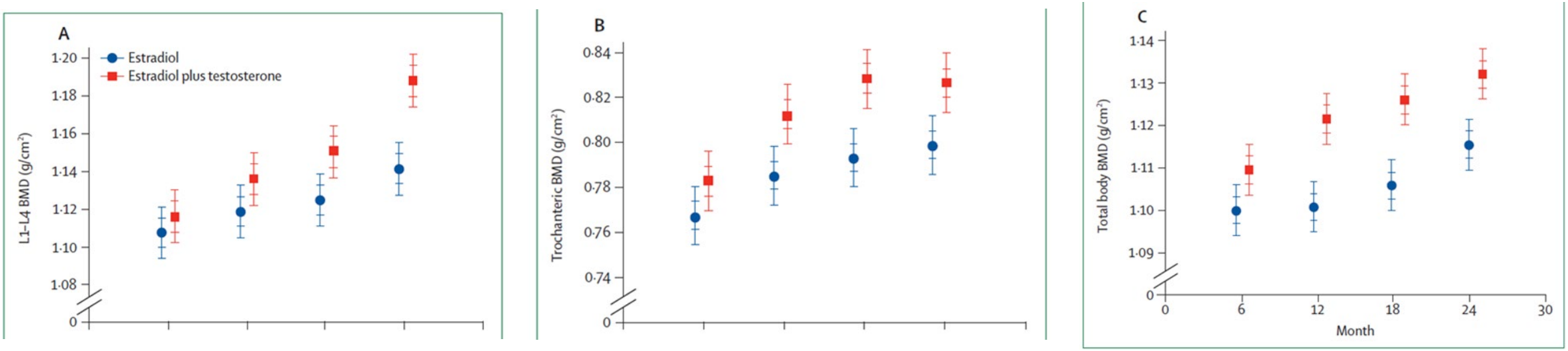
Rariy CM, et al. J Clin Endocrinol Metab. 2011; 96(4): 989-996.

TTH Improves BMD

Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality ☆

Susan R. Davis*[a], Philip McCloud[b], Boyd J.G. Strauss[c], Henry Burger[a]

[a]Prince Henry's Institute of Medical Research, 246 Clayton Road, Clayton, Victoria 3168, Australia
[b]Monash University, Clayton, Victoria 3168, Australia
[c]Body Composition Laboratory, Monash Medical Centre, 246 Clayton Road, Clayton, Victoria 3168, Australia



- Study: 34 PMP women, 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 T 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 women 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.

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 as long as control aromatization
  - 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 decreases invasive BC incidence, and decreases 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.

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 women treated with T pellets for hormone deficiency symptoms
- Study: 1267 pre/perimenopausal (23.2%) and PMP (76.8%) women, 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.

TTH Key Points and Practice Points

- TTh is safe and does not increase EC, BC, or CVD Risk
- TTh when added to TD E2 + OMP/VMP improves endothelial function and BMD to a greater extent than TD E2 + OMP/VMP
- A TD E2 0.025mg patch + OMP 200mg + TD T cream 1mg or T pellet 50-150mg (typically weight based 1.5-2.5mg/kg)
- Understand a woman's hormone metabolism and detoxification prior to starting hormone therapy, especially when adding T
- T metabolism, in both men and women, is complicated
- Serum is the default, urine adds comprehensiveness
- Similar to E2, follow-up testing and ongoing surveillance is a must

How do we translate this into clinical practice?

Maggie

Maggie is a 52-year old PMP female who seeks advice on MHT. Her last cycle was ~ 12-months ago and she has been miserable for the past 6-months. She has brain fog, hot flashes, night sweats, and complains of vaginal dryness. She has no energy, but feels anxious all the time and her mind cannot stop racing. She has trouble sleeping, waking multiple times.

She is happily married and has grown children. She is a physician and has a very busy practice. She has a normal body weight and BMI. She exercises regularly, she primarily runs with some minimal strength training 7d/week, 2x a day. She takes vitamin D 5000 IU/d, calcium 500mg/d, and a multivitamin after a recent BMD documented osteopenia.

Her PMH, FH, SH, and ROS are otherwise unremarkable. A recent mammogram was normal and a recent pap and pelvic exam were also normal.

Maggie's Initial Labs

Baseline Labs

- CBC: WNL
- Chemistry: WNL except for glycemic parameters
- FBS: 90, FI: 8, HbA1c: 5.7
- Thyroid: WNL
- Lipids: TG: 120, LDL-P: 1200 (< 1000), APO-B: 95 (moderate risk), ox-LDL: 100 (< 60 U/L), HDL: 50 (large and buoyant), TMAO: 10.1 (< 6.2 μM)
- hs-CRP: 2.5 (goal < 1.0)
- CaC scan: 75 (moderate plaque, moderate risk)
- CIMT: 0.8mm (goal ≤ 0.5mm)
- GXT: normal

Pertinent Hormone Labs

- SHBG: 20nmol/L (17-124)
- DHEA-S: 150mcg/dL (100-495)
- Vitamin D: 75ng/mL
- FSH > 100mIU/L
- LH: > 55mIU/L
- Total E2: < detectable (LC-MS/MS)
- Total T: < detectable (LC-MS/MS)
- Progesterone: < detectable (LC-MS/MS)
- Prolactin: 7ng/dL (2-20)

Maggie: What Do We Think?

- She is a symptomatic PMP woman with osteopenia, subclinical ASHD, HPA-axis dysfunction, and gut dysbiosis
  - **Symptoms**: hot flashes, night sweats, vaginal dryness, brain fog, no energy
  - **Signs**: VVA, osteopenia
  - **Tests**: insulin resistance, undetectable sex hormones, normal pap, normal mammography
  - **Hormone tests**: validated 4-spot dried urine test with cortisol and cortisol metabolites

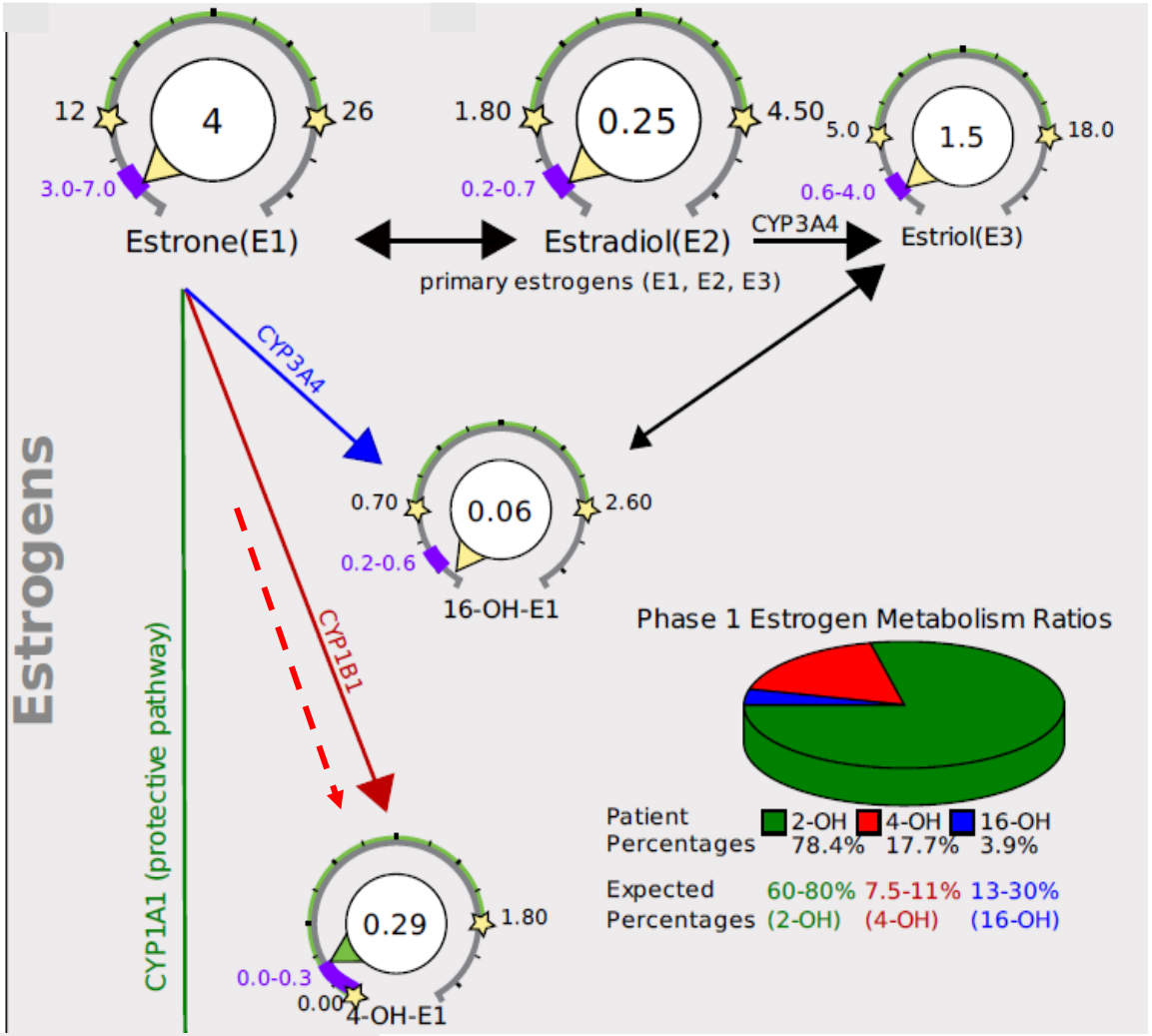
Maggie's E-Metabolism

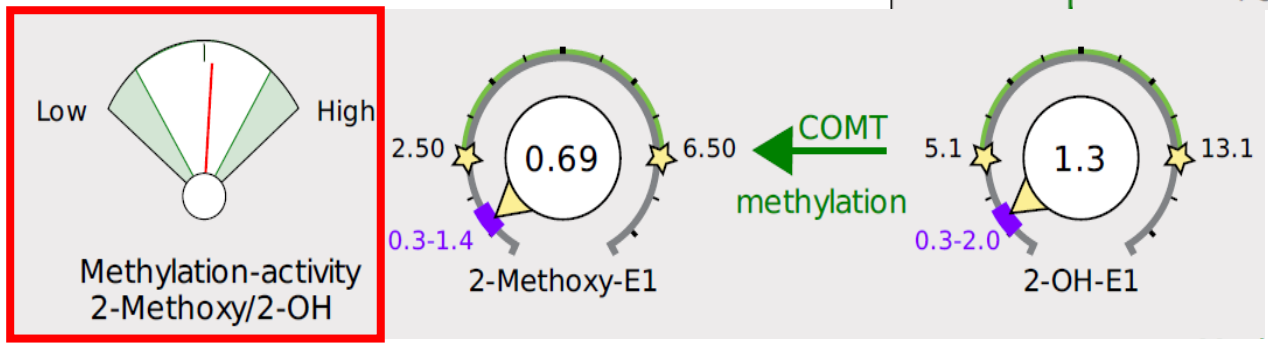
Pertinent Labs

- FSH > 100mIU/mL
- LH: > 55mIU/L
- E2, T, and Pg are not detectable (LC-MS/MS)

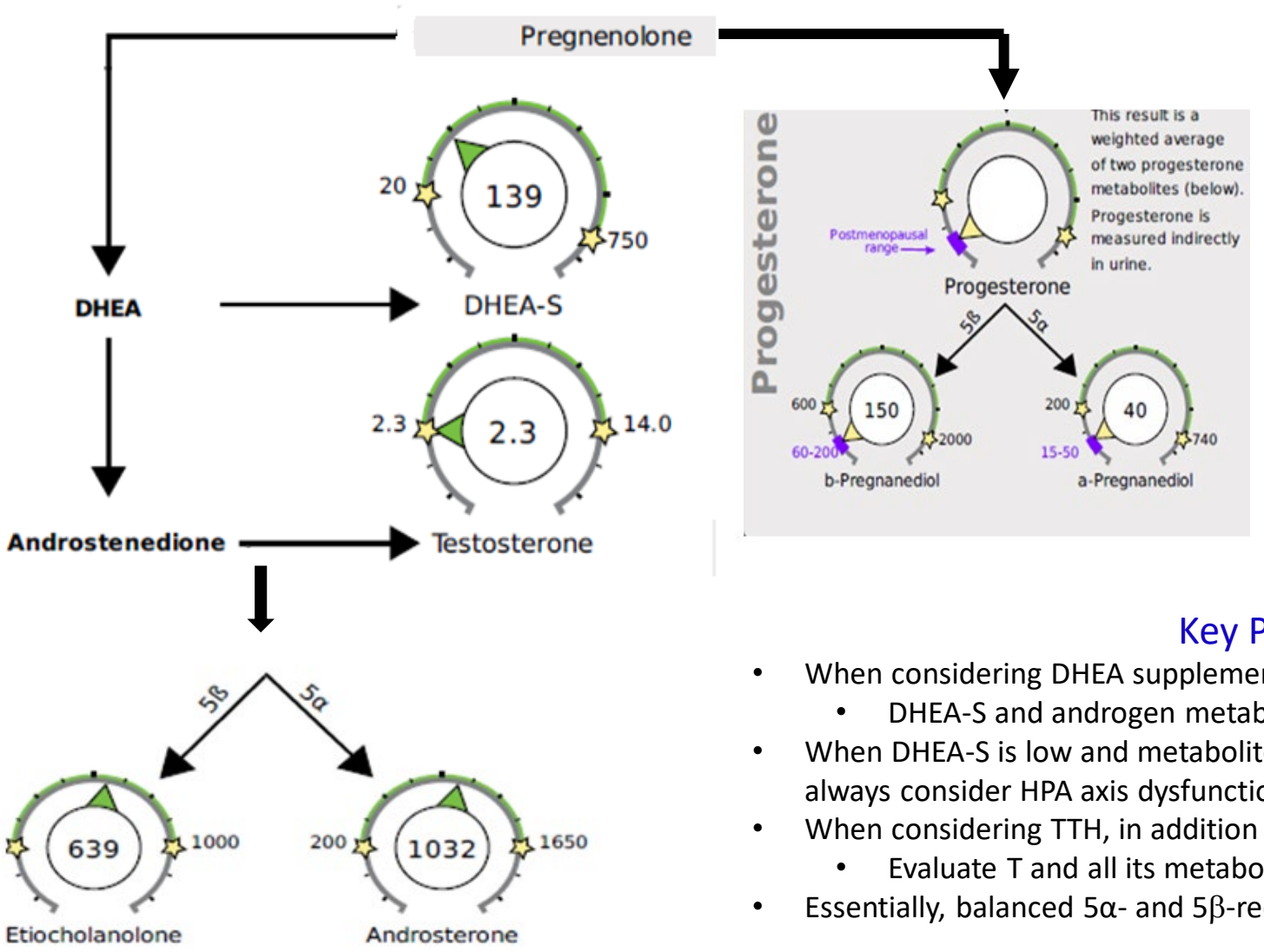
E Metabolism

- Trend toward favoring 1B1 pathway
- Methylation activity appears adequate





Maggie's Androgens, P4, 5α- and β-reductase

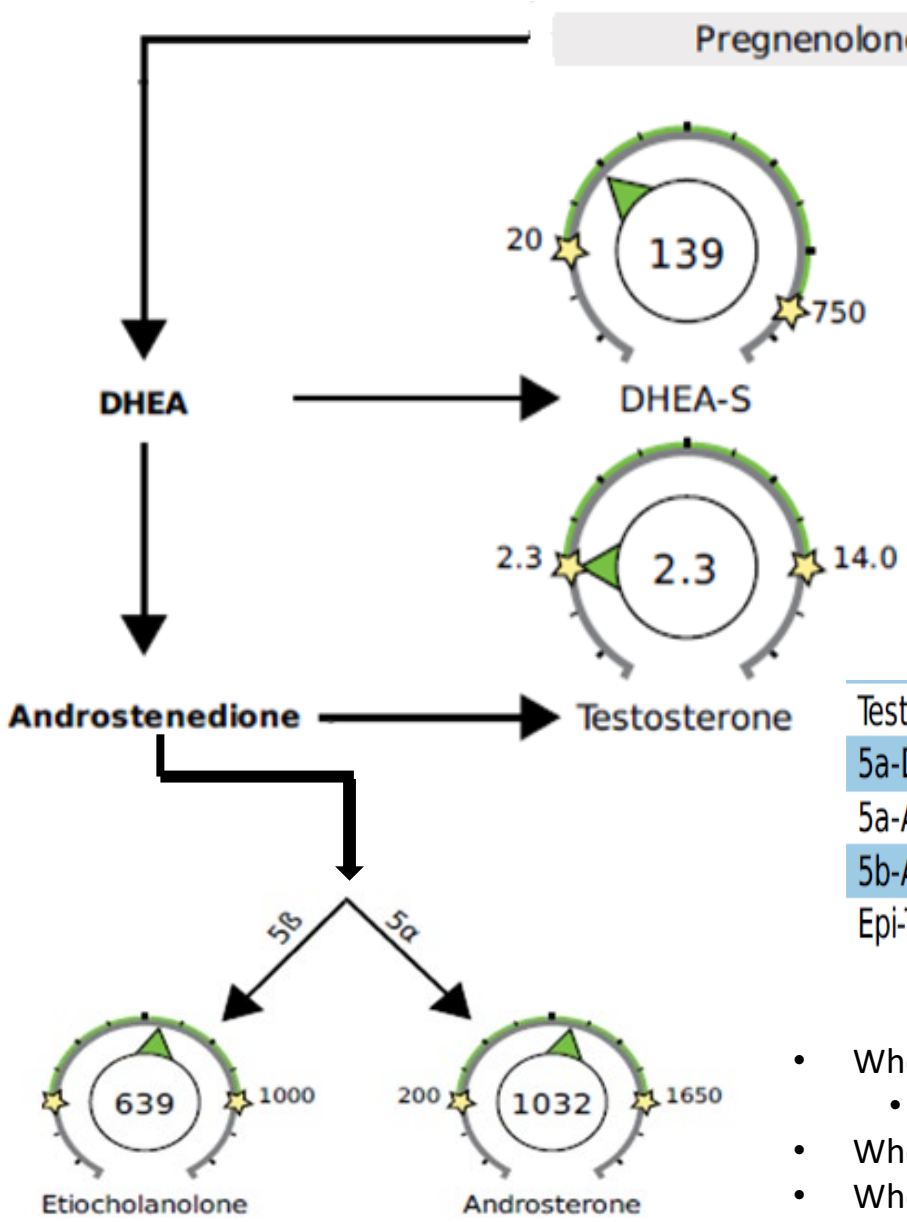


Androgen metabolites

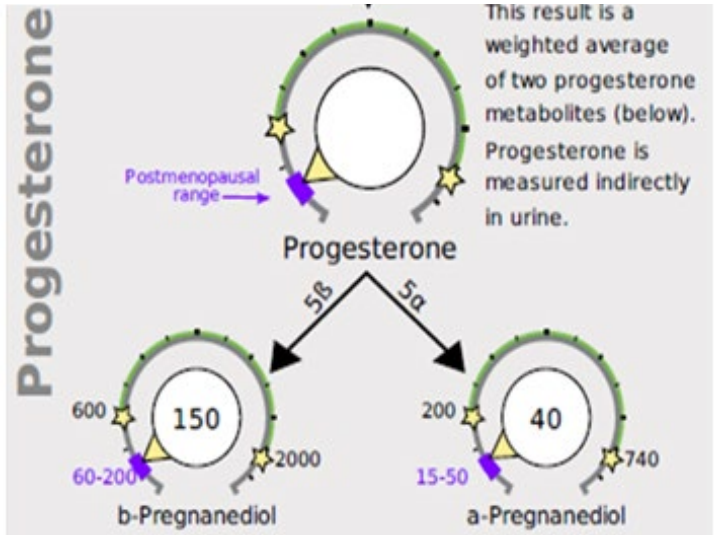
Key Points

- When considering DHEA supplementation: evaluate
  - DHEA-S and androgen metabolites (produced by both, DHEA and T)
- When DHEA-S is low and metabolites are normal or high, consider inflammation and always consider HPA axis dysfunction
- When considering TTH, in addition to serum
  - Evaluate T and all its metabolites when deciding on need for T, as well as T dose
- Essentially, balanced 5α- and 5β-reductase activity

Maggie's Androgens, P4, 5α- and β-reductase



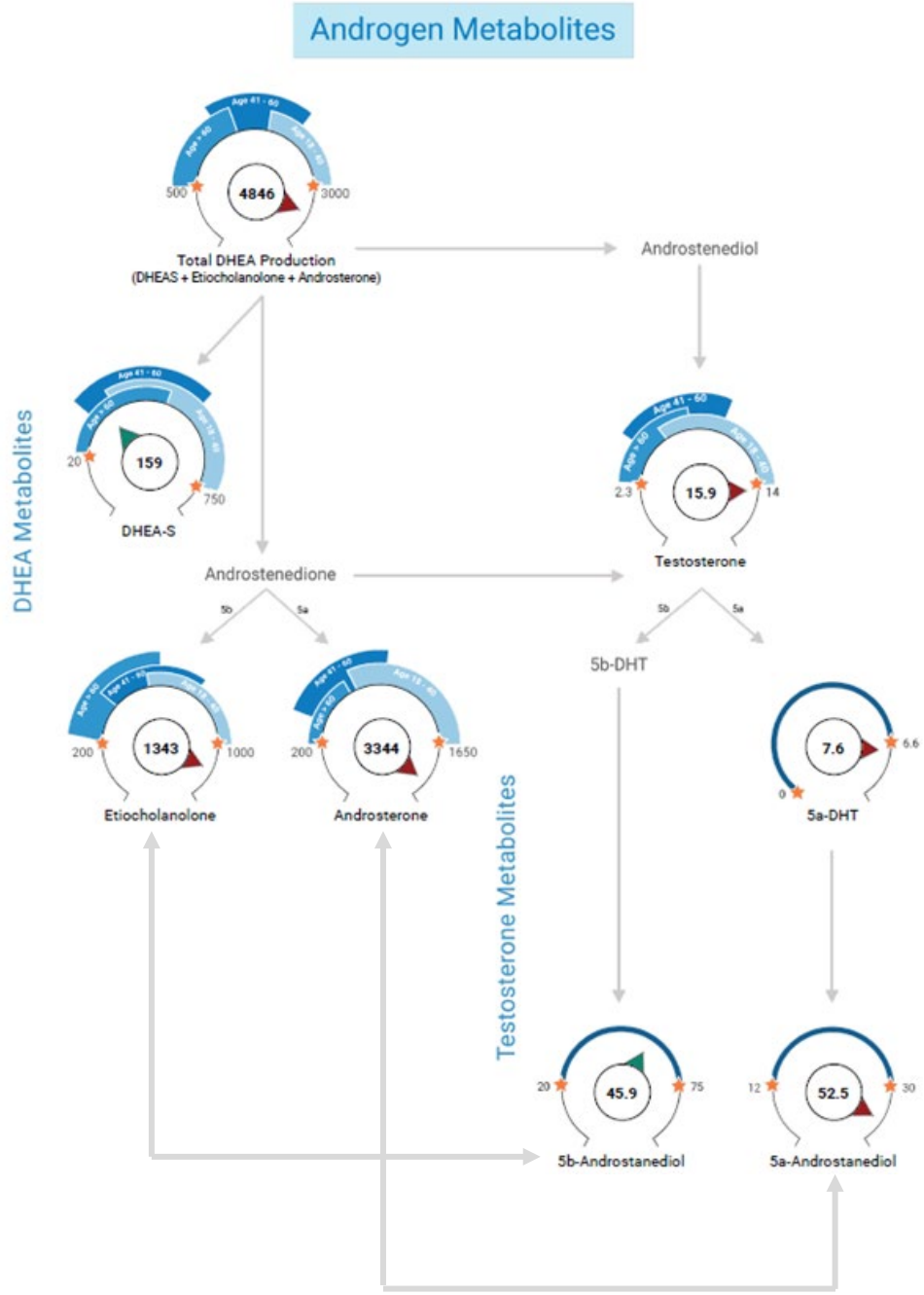
Androgen metabolites



Testosterone	Low end of range	2.3	ng/mg	2.3 - 14
5a-DHT	Within range	2.7	ng/mg	0 - 6.6
5a-Androstanediol	Within range	19.0	ng/mg	12 - 30
5b-Androstanediol	Within range	41.8	ng/mg	20 - 75
Epi-Testosterone	Below range	1.7	ng/mg	2.3 - 14

Key Points

- When considering DHEA supplementation: evaluate
  - DHEA-S and androgen metabolites (produced by both, DHEA and T)
- When DHEA-S is low and metabolites are normal or high, consider inflammation
- When considering TTH, in addition to serum testing, dried urine offers comprehensiveness
  - Evaluate T and all its metabolites when deciding on need for T, as well as T dose
- Essentially, balanced 5α- and 5β-reductase activity



Androgen Metabolism

Maggie's Hormone Treatment Plan

- Estradiol: TD E2 patch 0.025mg/d
  - Vaginal E3: 0.5mg/gm; apply 1 gram vaginally QHS x 2 weeks, then twice a week x 2 weeks, then PRN
- Progesterone: 200mg/d OMP QHS
- Testosterone: 1.0mg/d cream
- Nutraceuticals: DIM BID, Multivitamin, Complex B-vitamins
- Follow-up testing after 3 treatment months:
  - 4-spot dried urine for: hormones + metabolites, cortisol + metabolites
  - Blood for: CBC, CMP (albumin), FSH, LH, SHBG, total T (LC-MS/MS)

Maggie's 4-Month Follow-Up

Maggie feels great. Her brain fog is gone. The hot flashes and night sweats are gone, as is her vaginal dryness. Her energy levels are back to baseline (she is exercising less) and she is no longer anxious. She now gets 8-hours of restful sleep without awakening during the night.

She is exercising once a day, alternating running and strength training. She has starting taking a yoga class on the weekends with her husband and is enjoying it. She takes one full day off a week from exercising.

She is eating a healthier diet, with more vegetables and plant-based protein sources. The animal protein she eats is all grass-fed and organic. She gets about 20-25 grams of fiber a day. She has been compliant with the treatment plan.

Maggie's 4-Month FU

FU Labs

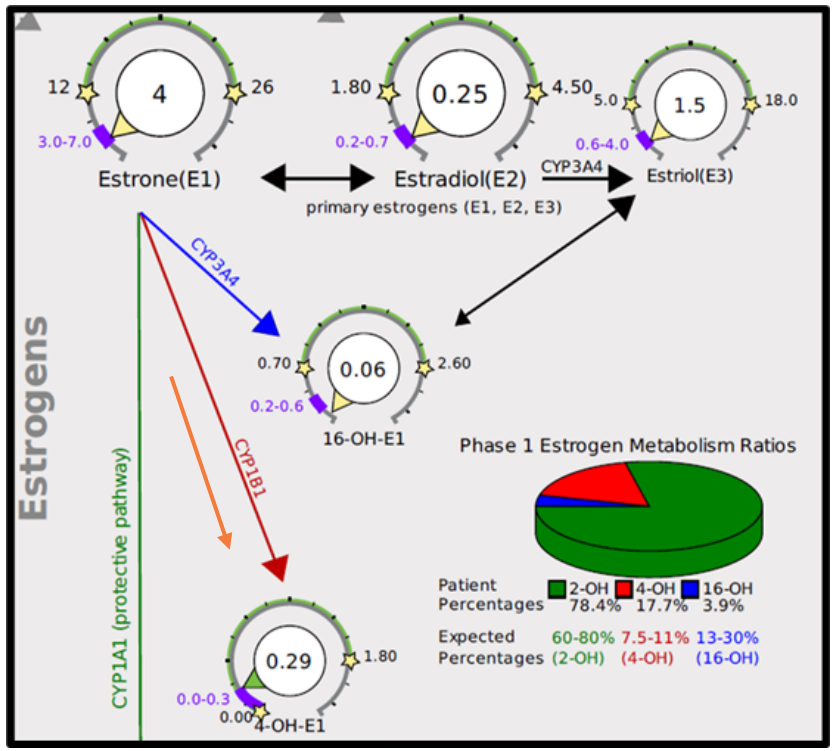
- CBC: WNL
- Chemistry: WNL
- FBS: 68, FI: 6, HbA1c: 5.2
- Thyroid: WNL
- Lipids: TG: 75, LDL-P: 600 (< 1000), APO-B normal, HDL: 50 (large and buoyant)
- hs-CRP: 1.1

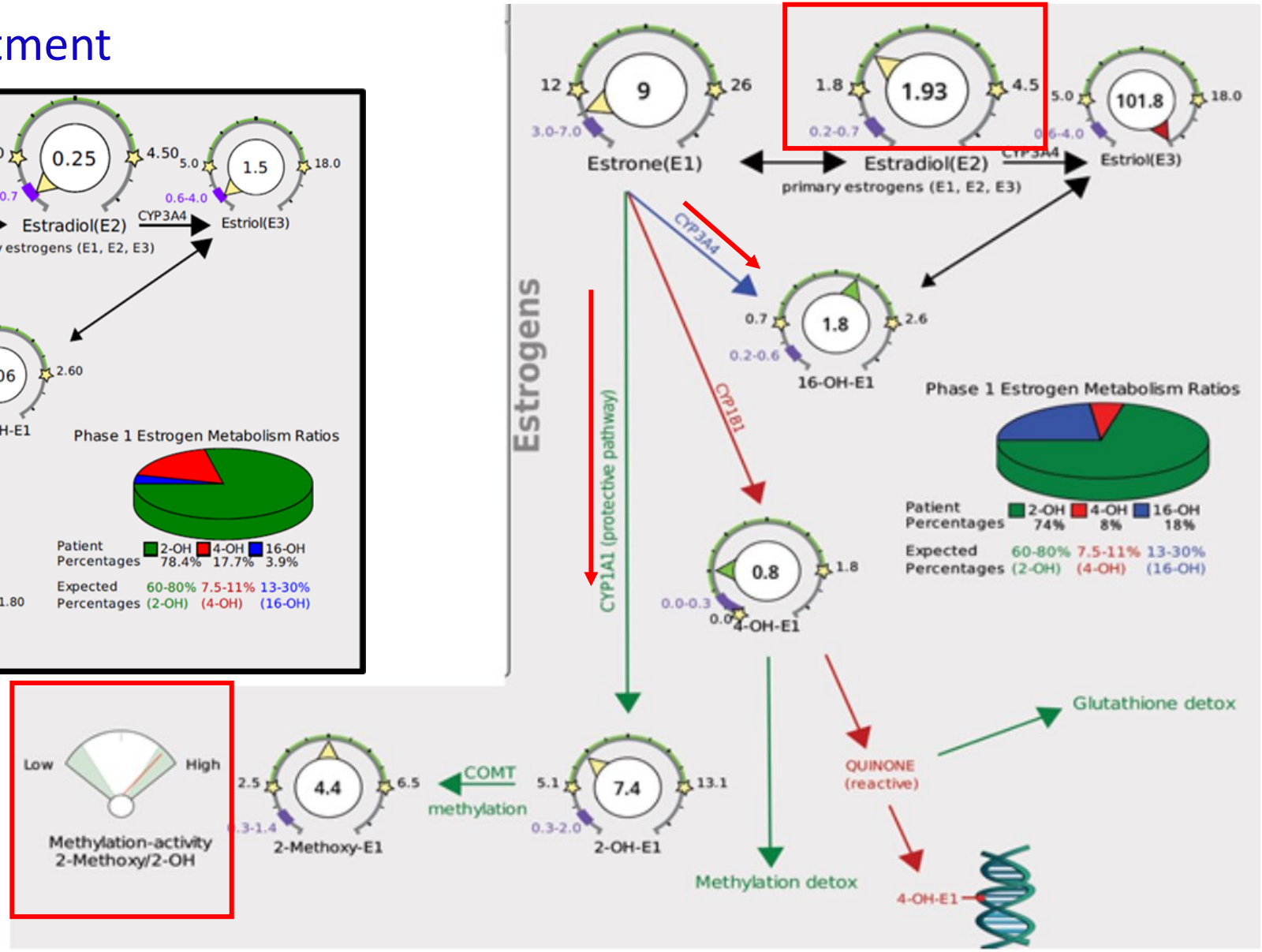
FU Hormone Labs

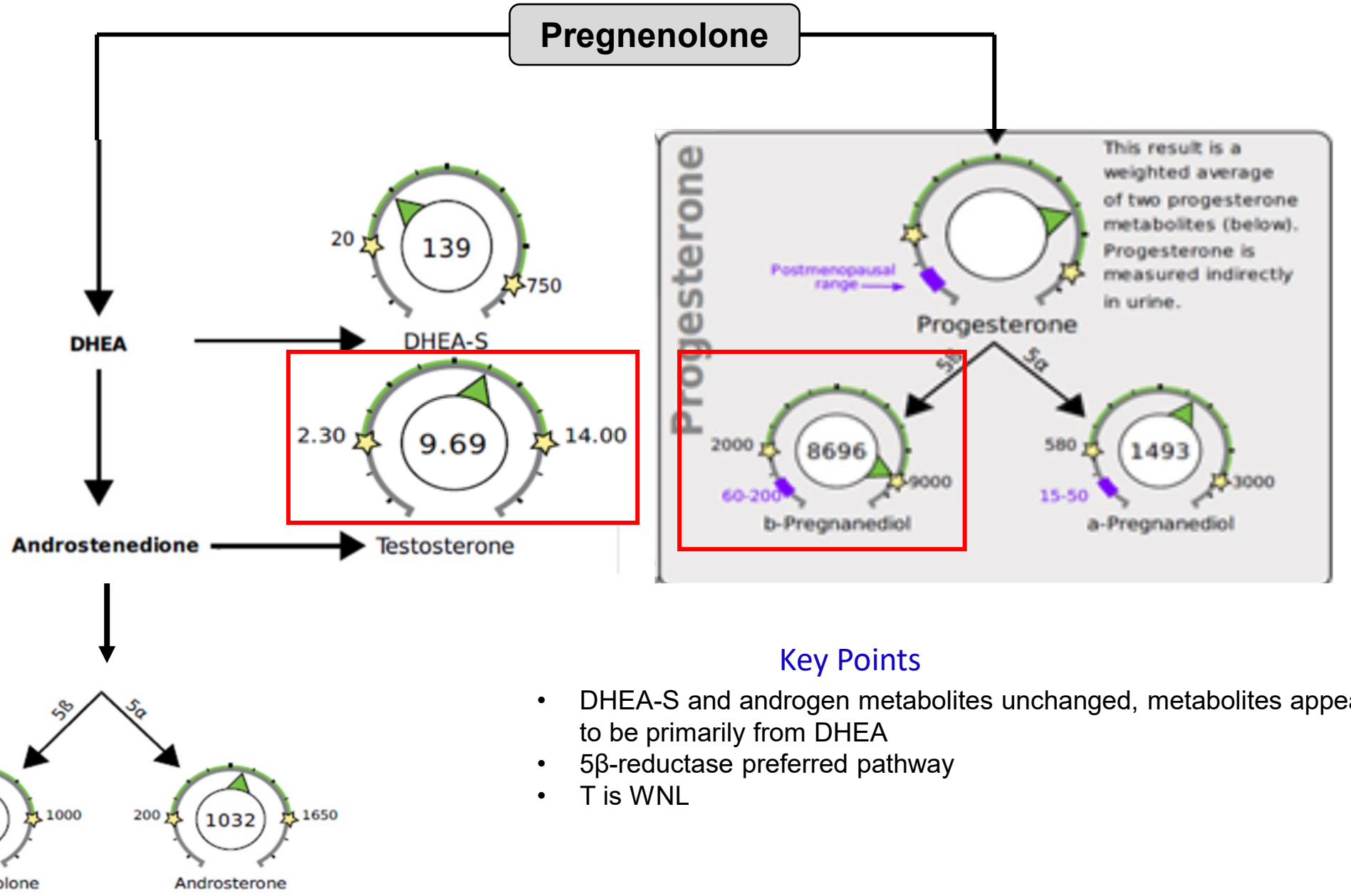
- FSH: 45mIU/L (25.8-134.8) ⬇
- LH: 25mIU/L (PMP: 10-54.7) ⬇
- SHBG: 30nmol/L (17-124) ⬆
- DHEA-S: 175mcg/dL (100-495)
- Vitamin D: 75ng/mL
- Total E2: 50pg/mL (LC-MS/MS) ⬆
- Total T: 40ng/dL (2-45) (LC-MS/MS) ⬆

Maggie's 4-Month FU

Pre-treatment







Key Points

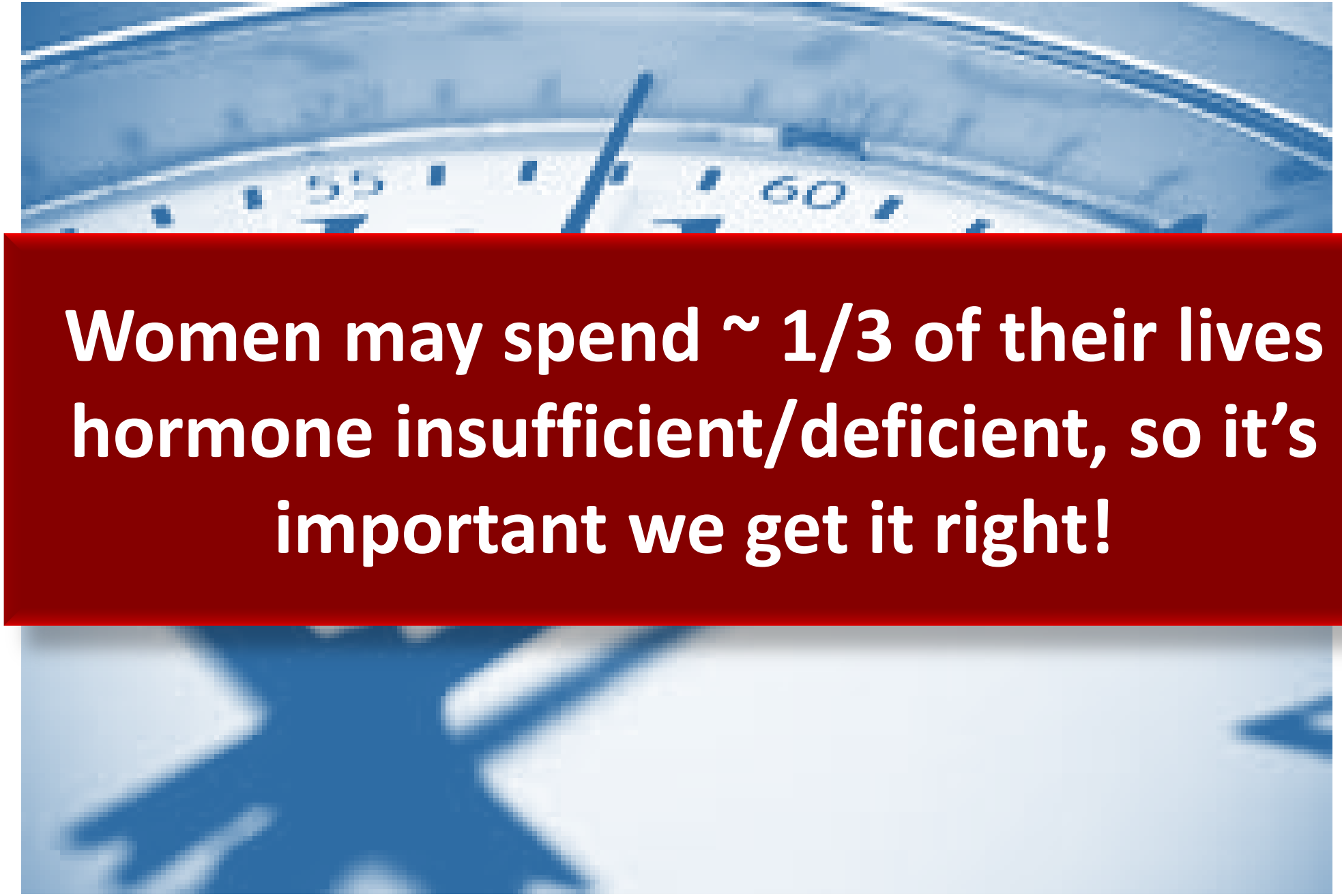
- DHEA-S and androgen metabolites unchanged, metabolites appear to be primarily from DHEA
- 5β-reductase preferred pathway
- T is WNL

MHT Key Points

- TD E2, oral/vaginal Pg, and TD/vaginal/pellet T therapies improve symptoms AND clinical outcomes
  - TD E2**:** improves VMS, VVA, BMD, sexual function, CV outcomes; cognition data is mixed; decreases BC incidence and mortality; TD E2 0.025mg/d patch, gels are product specific and not FDA-approved for BMD
  - Pg: E2's physiologic partner, necessary to balance E2's proliferative effects; important in maintaining BMD; improves VMS (300mg); OMP 200 or 100mg, VMP 100mg or 45mg
  - T: when added to E2 and Pg improves BMD to a greater extent than E2 and Pg alone; improves sexual function, VMS and VVA (may be due to E2 aromatization), DOES NOT increase BC, EC, or CVD risk; TD gels/creams up to 10mg/d, pellets 50-150 every 3-4 months
  - Compounded creams probably work, but no data

Final Thoughts

- Start MHT as close to menopause as possible, continue for at least 10-years with ongoing risk stratification, surveillance, and follow-up testing
- Start low, go slow, and set expectations
- A TD E2 0.025mg/d patch + OMP 200mg QHS + 1.0mg TD T is a good place to start, is evidence-based, and improves clinical outcomes; however, check metabolomics for optimal dosing
- Learn and understand hormone metabolomics, it is essential to a successful hormone practice
- Ask yourself: are your decisions evidence-based?
- Are you questioning the absolutes and asking: where is the evidence?



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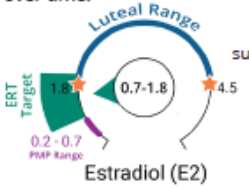
Can serum or DUTCH, as a standalone test, effectively monitor HRT? ✔ Yes ✘ No ? Maybe

Oral Progesterone (OMP)	Estradiol (E2) Patches	E2 Gels & Creams (Skin)	Vaginal E2 & Testosterone (T)	Vaginal Progesterone (Pg)	Transdermal (TD) Testosterone	Testosterone Injections & Pellets
✔ DUTCH	✔ DUTCH	✔ DUTCH	✔ DUTCH	✘ DUTCH	? DUTCH	? DUTCH
The DUTCH Test® provides useful feedback when using OMP in women with PMP sleep disturbances. 5a (more active) and 5b metabolites are measured to individualize OMP dosing. OMP's sleep effects are via its 5a metabolites, predominately allopregnanolone binding to the GABA receptor. No lab test reflects OMP's effect on the endometrium.	Values between the top of the postmenopausal range and the lower limit of the premenopausal range correlate with patient clinical improvement (bone density, hot flash relief, etc.). Doses that push levels to the middle of the premenopausal range and beyond may be excessive. DUTCH is preferred over serum because in addition to metabolites, dried urine averages out the daily up and down E2 patterns. This is particularly helpful with gels and creams that may have serum values that change rapidly over time.  The aggregate clinical data suggests that a serum (LC-MS/MS) E2 level of ~20-40pg/mL improves clinical outcomes (VMS, VVA, BMD). This approximates a DUTCH value of ~ 0.7-1.8ng/mg.		The DUTCH Test® is unique in that it removes potential contamination, and monitoring is helpful with E2 and T. Very low doses may impact local tissue without increasing lab values. For local (not systemic) E2 therapy, keep urine E2 in PMP range.	Pg is measured indirectly in urine by measuring pregnanediols. These metabolites may be underrepresented when Pg is taken vaginally. Serum Pg seems to increase to a higher degree than urine metabolites with vaginal Pg application.	Levels generally parallel changes in serum and clinical outcomes (increased lean body mass, erythrocytosis, etc. in men). Epi-testosterone (Epi-T) values can be used to assess gonadal suppression due to TRT (Epi-T levels in men decrease as TRT increases and are <10ng/mg with complete suppression).	Injections and pellets increase levels, as expected, but the increase may exceed what is seen in serum testing. DUTCH allows for monitoring both the dosing of hormones as well as metabolic patterns.
			Vaginal E2, Pg, and T are systemically absorbed. If placed in the top 1/3 of the vagina, a higher dose will get to the uterus (uterine 1st pass effect), which may be helpful for Pg, but not E2.		Urine testosterone does not correlate as reliably to T serum values, compared to E2 and other tests. Urine testing is best suited as a complimentary test to serum for T and should not be used solely for TRT decisions.	
✘ SERUM	✔ SERUM	? SERUM	✔ SERUM	? SERUM	✔ SERUM	✔ SERUM
Results go up and down quickly. If taken at bedtime, levels return to baseline within a few hours. Results can also be inaccurate due to progesterone metabolites cross-reacting with immunoassay tests.	Serum testing is well suited for use with these types of therapies. Results increase with increased dosing in a fairly linear fashion. Most recommendations are to push serum E2 levels to 20-40pg/mL for clinical impact.	The only published data for E2 creams shows serum results move up and down within a few hours, so serum testing can easily underestimate clinical impact. DUTCH results average out the daily up and down pattern and may be a better option.	Serum results rise quite dramatically with what may seem like modest doses due to the high uptake of hormones across the mucosal membrane. However, values may rise and fall quickly, so be careful with the interpretation of both low and high results.	Serum values increase with dosing and likely represent systemic exposure to Pg. However, the uterine first-pass effect loads the uterus with high levels of Pg (which may be desirable) and serum does not reflect uterine hormone levels.	A great deal of published research shows that serum levels reflect clinical changes in both men and women taking TD T. Be aware of potential up and down patterns throughout the day, but serum is the best tool for monitoring doses of TD T in both men and women.	Serum testing is well suited for use with these types of therapies. Results increase with increased dosing in a fairly linear fashion. Test injections halfway between doses or right before a dose.

✘ SALIVA	The literature does not support salivary testing's use for monitoring TD hormone creams. The saliva data is limited and, in fact, there are no saliva testing outcome studies using TD creams, injections, estradiol patches, oral estradiol, or vaginal hormones. While salivary testing is the gold standard for free cortisol measurement, avoiding its use for monitoring HRT is advised. For situations where saliva testing may parallel the clinical impact, DUTCH or serum testing are better options (see above).
✘ Oral Estradiol, Estradiol Pellets, or Sublingual Hormones	Though not recommended, if you choose to use either oral estradiol or estradiol pellets, serum testing can monitor both, whereas urine should only be used with pellet therapy. Sublingual hormones may be used in some situations but lab monitoring is not helpful in optimizing doses.
✘ Transdermal Progesterone	In PMP women, the evidence does not support TD Pg's use to protect the endometrium. When prescribed, laboratory monitoring is not helpful for TD Pg dosing.

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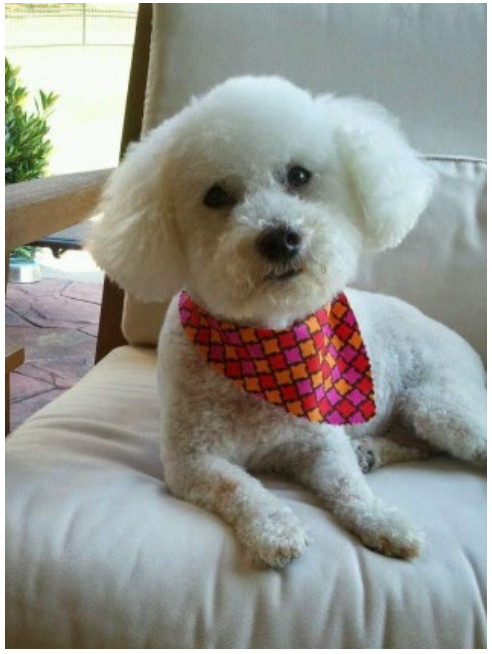

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