Women's Health and Hormonal Axis Part 2

Joel Evans, MD

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Perimenopause

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Perimenopause

- Transition phase from the onset of cyclic night sweats or other characteristic changes in regularly menstruating women until one year past final menstruation
- Average timeframe 4-8 years, can start in mid 30's, usually starts in mid 40's

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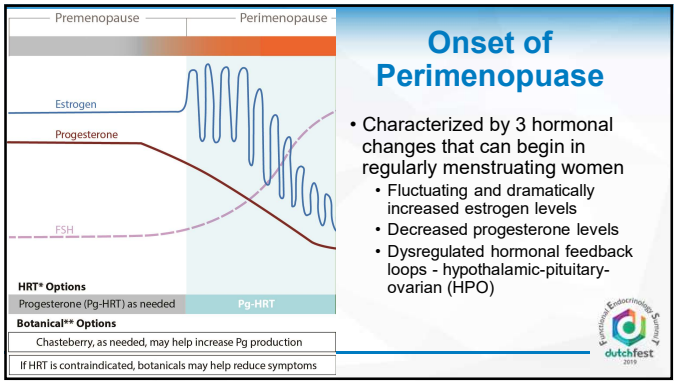

Onset of Perimenopuase

- Characterized by 3 hormonal changes that can begin in regularly menstruating women
  - Fluctuating and dramatically increased estrogen levels
  - Decreased progesterone levels
  - Dysregulated hormonal feedback loops - hypothalamic-pituitary-ovarian (HPO)

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Perimenopause: Hormonal Changes

- Estradiol: Not just what you think!
  - E fluctuates throughout this transition period: Higher than reproductive age levels and stays high for longer periods of time before decreasing
  - Many perimenopausal symptoms 2^0 to higher estrogen levels
  - Lots of data to support higher E's during transition

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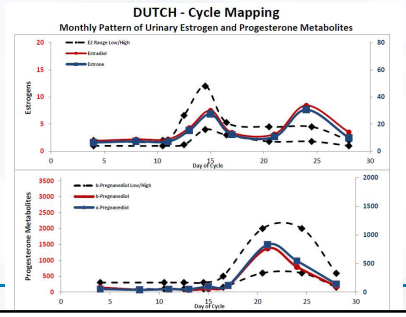
Typical Perimenopause Menstrual Cycles



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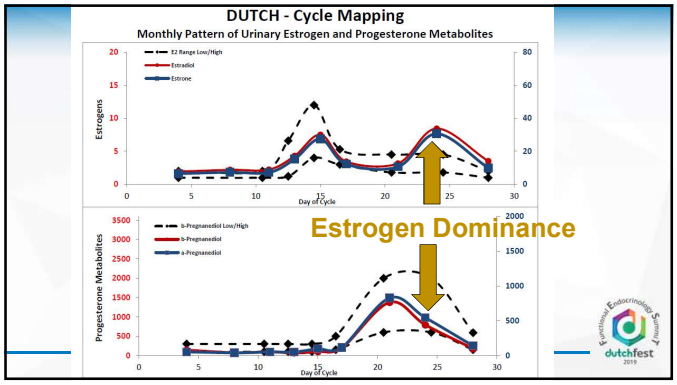

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Perimenopause: Hormonal Changes

- Progesterone levels fall, but why?
  - Decreased progesterone within normal-length ovulatory cycles
  - Shortened luteal phase lengths within ovulatory cycles
  - More frequent anovulatory cycles
  - Less studies than for E2, and none are population based

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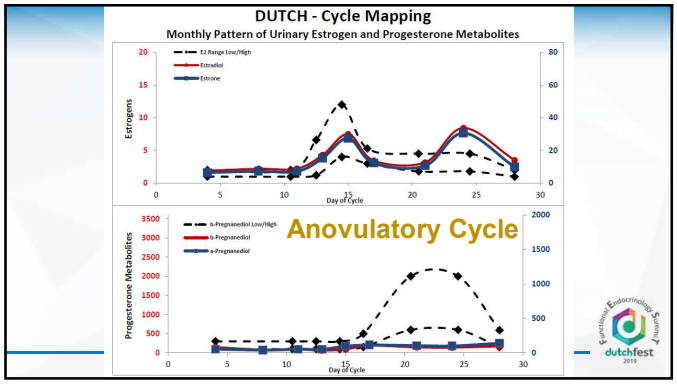

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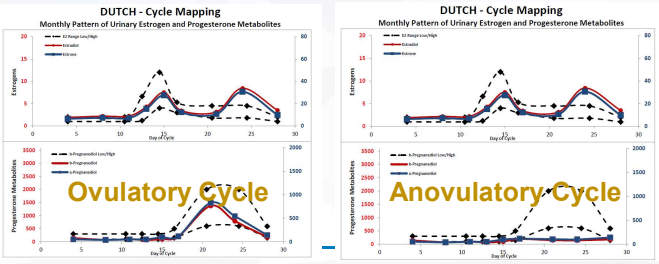
Perimenopausal women may live between these states of estrogen dominance



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The STRAW staging system

Final Menstrual Period (FMP)

Stages:	-5	-4	-3	-2	-1	0	+1	+2
Terminology:	Reproductive			Menopausal Transition			Postmenopause	
	Early	Peak	Late	Early	Late*		Early*	Late
				Perimenopause				
Duration of Stage:	variable			variable		(a) 1 yr	(b) 4 yrs	until demise
Menstrual Cycles:	variable to regular	regular		variable cycle length (>7 days different from normal)	≥2 skipped cycles and an interval of amenorrhea (≥60 days)	Amen = 12 mos	none	
Endocrine:	normal FSH		↑ FSH	↑ FSH			↑ FSH	

*Stages most likely to be characterized by vasomotor symptoms ↑= elevated

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Perimenopause: Hormonal Summary

- During early perimenopause, estrogen and progesterone are changing in **opposite** directions – Estrogen Dominance!
  - In late perimenopause both are low
- These hormonal changes (↑ E and ↓er P) may be expected to increase a woman's risk for endometrial and breast cancer, but do they? Not a lot of data

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Perimenopause: HPO Dysregulation

- Hormonal changes not just from "aging ovary"
- Inhibin B: key to feedback dysregulation
  - An ovarian hormone produced in developing follicle granulosa cells or corpus luteal lutein cells
  - Acts to suppress FSH via negative feedback (NFB) to hypothalamus
  - During perimenopause, this NFB fails, predominantly at the follicular-luteal phase transition
  - When each ovary has less than ~ 100 follicles, inhibin B decreases and can no longer hold FSH "in check"
- Rising FSH increases E2 and can cause a second luteal, out of phase, peak (LOOP)

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Perimenopause: Symptoms

- Vasomotor symptoms (VMS)
  - Hot flushes/flashes (HFs)
    - FSH independent predictor likelihood of vasomotor symptoms: positive correlation
    - Estradiol levels have no correlation to presence and or severity
    - Occurs in ~ 80% women increasing from early to late perimenopause
    - Can last up to 10 years
  - Night sweats are HFs that occur at night and disrupt sleep

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Perimenopause: Symptoms

- VMS and CVD Important Fact
  - Frequent VMS that start later during perimenopause have an increased CVD risk, as opposed to earlier onset VMS
  - VMS linked to reduced heart rate variability

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Perimenopause: Symptoms

- Vasomotor Risk Factors
  - African American and Native Indian women have highest VMS reporting
  - Elevated BMI associated with worse HF when perimenopausal, but fewer and milder HF when menopausal
  - Cigarette smoking
  - Anxiety and depression
- Most severe HFs occur if African American or high BMI

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Perimenopause: Symptoms

- Sleep and mood changes
  - Women with Met-S poor sleep efficiency
  - Difficulty falling asleep, staying asleep, early awakening
  - Strongly associated with vasomotor symptoms
  - Mood is impacted by life stresses

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Perimenopause: Symptoms

- Vaginal and sexual symptoms
  - Vaginal dryness and atrophy, dyspareunia, urinary symptoms
  - Typically require long term treatment
- Bleeding
  - Bleeding patterns vary and it can be difficult distinguishing between “normal” and “abnormal”

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Perimenopause FM Treatment Approach

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Non-HRT Treatments

- Lifestyle and Diet
  - Address HPA axis - test
    - Sleep, Prayer/Meditation
    - Vitamins B's, C, multivitamin
  - Diet and GUT testing if appropriate
    - 5 R program
    - Avoid alcohol, caffeine, sugar
  - Exercise
- Treat inflammation
  - Fish oil, Curcumin
- Metabolism
  - Thyroid
    - Iodine, selenium, meds
  - Obesity/ IR/Met-S
- Optimize estrogen metabolism
  - Foods, nutraceuticals
- Acupuncture
- Phytoestrogens/botanicals

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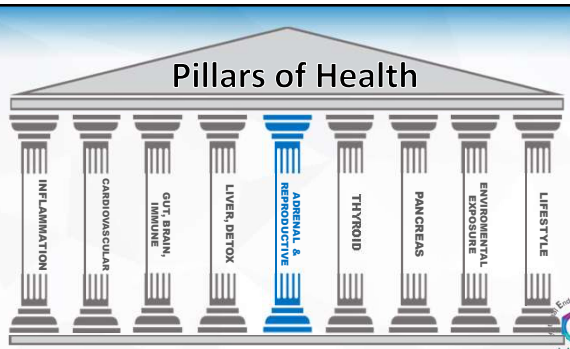
Pillars of Health



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Perimenopause: Non-HRT Treatments

- Lifestyle
  - Address HPA axis - test
    - Sleep, Prayer/Meditation
    - Vitamins B's, C, multivitamin
  - Diet and GUT testing if appropriate
    - 5 R program
    - Avoid alcohol, caffeine, sugar
  - Exercise
- Treat inflammation
  - Fish oil, Curcumin
- Metabolism
  - Thyroid
    - Iodine, selenium, meds
  - Obesity/ IR/Met-S
- Optimize estrogen metabolism
  - Foods, nutraceuticals
- Acupuncture
- **Phytoestrogens/botanicals**

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Perimenopause Treatment: Botanicals

1. HPA axis support
   - Reference HPA axis discussion
2. Phytoestrogens and soy isoflavones (direct, estrogenic impact)
   - Phytoestrogens – black cohosh, red clover, sage, Siberian rhubarb, non-GMO soy
   - Soy isoflavones – genestein, daidzein
3. Support natural hormone production
   - Chasteberry – may increase progesterone production
4. Support for menopausal symptoms other than hot flashes
   - Poor sleep (passionflower, magnolia, scutellaria, hops, lavender, valerian, Eschscholzia
   - Mood – St john's Wort, Melissa, lavender, passionflower (also non-botanicals –5-HTP, pregnenolone, L-theonine, glycine)

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Citations: Perimenopause

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- Prior JC. Progesterone or progestins as menopausal ovarian hormone therapy: recent physiology-based clinical evidence. *Curr Opin Endocrinol Diabetes Obes*. 2015; 22: 495-501
- Brown SB, Hankinson SE. Endogenous estrogens and the risk of breast, endometrial, and ovarian cancers. *Steroid*. 2015; 99: 8-10

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- Delamater L, Santoro N. Management of the Perimenopause. *Clin Obstet Gynecol*. 2018; 61(3): 419-432

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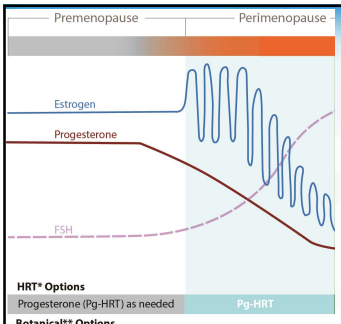

Eventually Patient May Need ERT, But Not Yet!

- In the estrogen dominant stage of perimenopause, Pg-HRT may be helpful
- As E2 drops and she heads towards menopause, ERT may be appropriate as well

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Progesterone HRT in Perimenopause

Progesterone Functions

- May decrease breast cancer progression via progesterone receptor's (PR's) modification of the estrogen receptor-α (ER- α) genetics
- Involved in ovulation initiation
- Inhibits uterine activity
- Induces enzymes involved in estrogen metabolism

Progesterone Effects

- Improves sleep
- Improves vasomotor symptoms
- Beneficial cardiovascular effects
- Improves bone density
- Decreases menorrhagia and dysmenorrhea
- Improves anxiety/mood swings

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Progesterone HRT in Perimenopause

- Oral micronized progesterone
  - Significantly decreases VMS when compared to placebo, also improves sleep and endothelial function
  - No 3-month negative CVD, VTE effects
  - 200-300mg days 8-28
- Transdermal (TD) progesterone
  - Minimal data to support efficacy in treating VMS
    - 60mg "nearly" reached statistical significance when compared to placebo
    - Trend towards greater VMS improvement with increasing transdermal dose
      - 20mg vs 40mg vs 60mg

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Menopause

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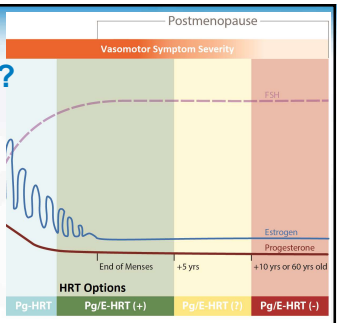
Menopause: We're Here, Now What?

- No more periods
  - >12 months definitive
- VMS likely increasing
- FSH and LH likely elevated
- Low E2 (<20pg/mL in serum)
- Low P (in non-cycling range)
- Low anti-Mullerian Hormone



If HRT is contraindicated, botanicals may help reduce symptoms

Bacon JL. *Obset Gynecol Clin North Am.* 2017; 44(2): 285-296

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Menopause: General Information

- Defined retrospectively as cessation of menses for 12 months
- Family history matters – so listen!
- **Primary indication for treatment - symptoms**
- Vasomotor symptoms continue for a variable period of time
  - VMS continue for > 1 year in 80% women and resolve in 4-5 years without treatment
  - VMS continue in ~ 10% for many years

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Menopause: General Information

- VMS correspond with increasing FSH levels, decreasing inhibin-B, AMH levels, very low antral follicle count, and decreased E2 levels
  - Increasing FSH and decreasing E2 for ~ 2 years
  - Next 3-6 years, FSH stabilizes, E2, inhibin-B, and AMH are all very low
- During menopause, estrogen production occurs in the ovarian stromal cells and peripherally, aromatizing androgens to estrogens
  - Most peripheral aromatization to estrogens occurs in adipose tissue
- Decreased follicles decreases ovulation leading to decreased progesterone, and increasing LH

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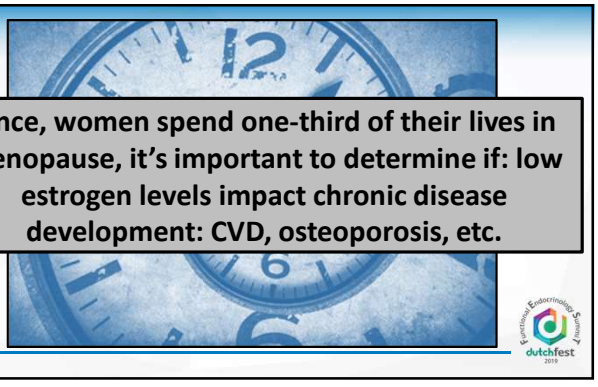

Since, women spend one-third of their lives in menopause, it's important to determine if: low estrogen levels impact chronic disease development: CVD, osteoporosis, etc.

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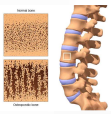
Menopause & Future Health Risks





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Comorbidities of Menopausal Changes

- Low Estrogen (E)

Due to levels naturally lowering at and beyond menopause

- High E, Low P

Due to perimenopausal estrogen dominance or ERT and the natural drop in P

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Comorbidities of Menopausal Changes

- Low Estrogen (E)
  - Cardiovascular Disease
  - Osteoporosis
  - Vaginal Atrophy, Incontinence
  - Cognitive Decline
  - Poor Quality of Life
- High E, Low P
  - Breast Cancer
  - Endometrial Cancer

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The Challenge of Safe, Effective HRT

Low Estrogen (E)

- Cardiovascular Disease
- Osteoporosis
- Cognitive Decline
- Vaginal Atrophy, Incontinence
- Poor Quality of Life

High E, Low P

- Breast Cancer
- Endometrial Cancer

How do we minimize these risks without increasing these?

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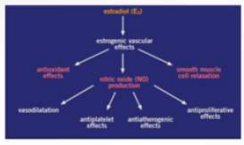
Comorbidities of Low Estrogen

- **Cardiovascular Disease**
- Osteoporosis
- Cognitive Decline
- Vaginal Atrophy, Incontinence
- Poor Quality of Life (hot flashes, etc.)



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Estrogen and CVD: The Facts

- General
  - Heart disease is the # 1 killer in women
  - In women > 50 years old, > 50% of deaths are cardiac related
  - Women with premature menopause or premature surgical menopause have a **higher risk of CVD if not given estradiol**
  - Lifetime Risk of developing CVD: 32% in women, 49% in men
  - In women, CVD lags behind men by ~ 10 years
  - Women have a worse prognosis after a 1st event when compared to men

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Estradiol and CVD: Summary

- Endogenous estradiol is cardioprotective. Low menopausal levels increases CVD risk
- Estrogen therapy in women less than 60 and within 10 years of menopause decreased cardiovascular events and all-cause mortality
- A must for women with premature or premature surgical menopause
- Progesterone does not increase or decrease CVD risk
- **The Timing Hypothesis – initiating ERT early may reduce CVD risks**

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Comorbidities of Low Estrogen

- Cardiovascular Disease (HRT helps)
- **Osteoporosis**
- Cognitive Decline
- Vaginal Atrophy, Incontinence
- Poor Quality of Life (hot flashes, etc.)

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Osteoporosis: General Information

- Globally, approximately 200 million have osteoporosis
- ~10 million in USA have osteoporosis, 44 million osteopenia
- 80% of those with osteoporosis are women
- 1 in 3 women > 50 will be diagnosed with an osteoporotic fracture during her lifetime
- A women's osteoporotic fracture risk = her combined breast cancer, uterine, and ovarian cancer risks
- Peak BMD (early adulthood) determines bone loss later in life.

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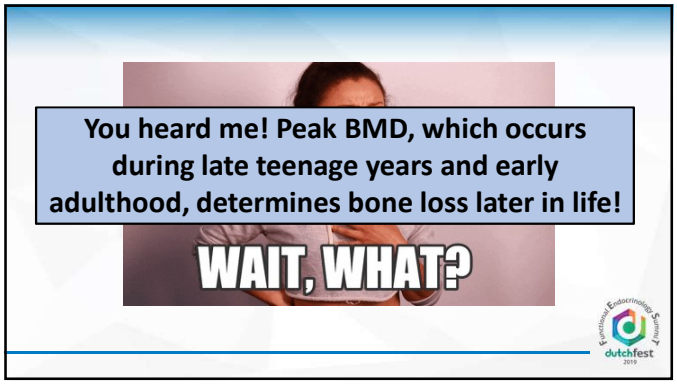

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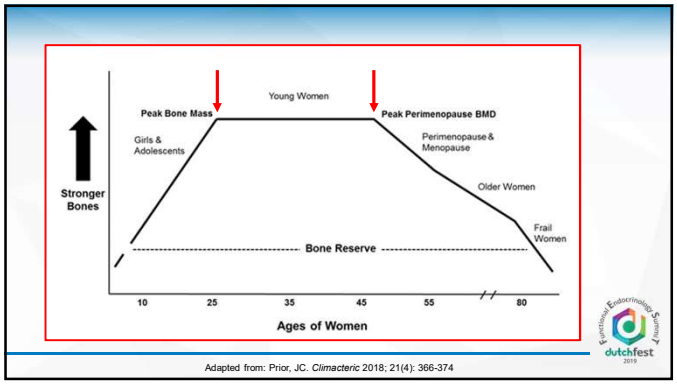

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HRT and Osteoporosis

- E2 should be considered 1st line therapy for osteoporosis
- E2 prevents osteoporosis & increases BMD in postmenopausal women
  - WHI showed less osteoporosis-related fractures, even in low risk women
  - In a meta-analysis (prevention and treatment) involving ~ 10,000 women, change in BMD was higher in opposed and unopposed estrogen groups
- **Withdrawing estradiol results in rapid bone loss**, and within 1 year most of the previous increased BMD accumulated over had disappeared
- Progesterone also helps synergistically (balance both for optimal BMD)

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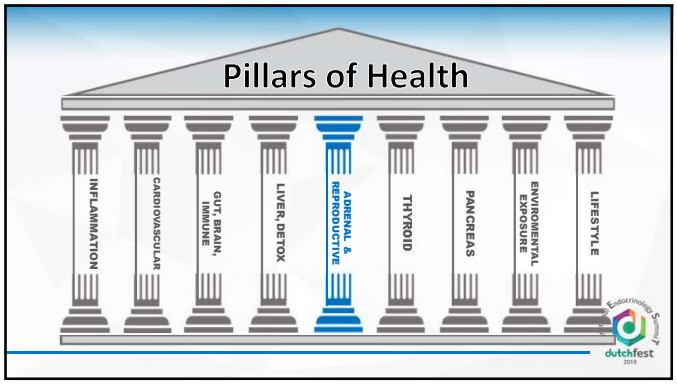

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Osteoporosis – Don't Forget the Pillars

- Hormones
  - Estrogen, progesterone
- Additional Support
  - Vitamin D
  - Vitamin K2MK7
  - Calcium
- Optimize gut health
- Manage stress
  - Sleep, meditation, etc
- No dairy: increases risk
- Moderate daily weight bearing exercises
- Anti-inflammatory diet
- Limit alcohol
  - Bone toxic
- No smoking
- Optimize body weight
  - Low BMI associated with increased fracture risk

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Comorbidities of Low Estrogen

- Cardiovascular Disease (HRT helps)
- Osteoporosis (HRT helps a lot!)
- **Cognitive Decline**
- Vaginal Atrophy, Incontinence
- Poor Quality of Life (hot flashes, etc.)

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Estrogen and Cognition Information

- Human studies on HRT and cognition are inconsistent
- Surgical Menopause is associated with cognitive decline
- Unclear whether low estrogen is a key contributor to age-related cognitive decline
- **Key Question – Does HRT help?**

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HRT and Cognition – Some positive studies

- Berent-Spillson, et al. (2015) used functional MRI testing to assess estradiol's **or** progesterone's effects on visual and verbal cognition
  - Compared to placebo, **estradiol** treatment had greater left prefrontal cortex activation, a region associated with **verbal** processing and encoding
  - Compared to placebo, **progesterone** was associated with changes in regional brain activation patterns during a **visual** memory task, with greater left prefrontal cortex and right hippocampus activation
- **Results point to a potential cognitive benefit of both estradiol and progesterone, but needs further study**

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HRT and Cognition

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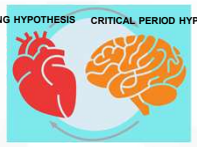
Estrogen Replacement and Cognition: The Data

There may be a "critical period" whereby HRT therapy has a positive effect on cognition, if given at or close to menopause onset

TIMING HYPOTHESIS CRITICAL PERIOD HYPOTHESIS



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Estrogen Replacement and Cognition: The Data

There may be a "critical period" whereby HRT therapy has a positive effect on cognition, if given at or close to menopause onset

TIMING HYPOTHESIS CRITICAL PERIOD HYPOTHESIS

More specifically, if you wait too long to initiate HRT, cognition outcomes are negative

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IT'S ALL ABOUT TIMING

The Timing Hypothesis: when to start HRT, when to stop

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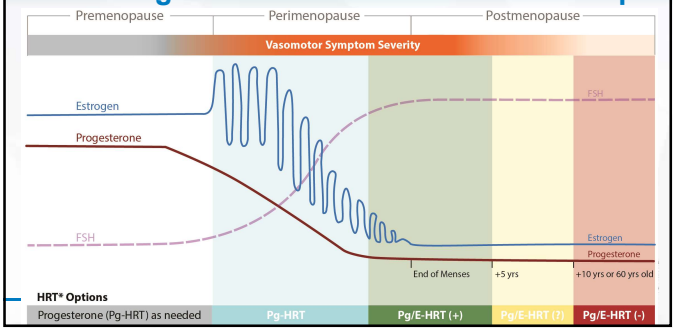
Minimizing HRT Risks: When to Initiate/Stop?



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Comorbidities of Low Estrogen

- Cardiovascular Disease (HRT helps)
- Osteoporosis (HRT helps a lot!)
- Cognitive Decline (Benefits unclear)
- Vaginal Atrophy, Incontinence (HRT helps)
- Poor Quality of Life - hot flashes, etc. (HRT helps)

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Where Are We?

- CVD prevention: treatment benefits up to 10 years and maybe longer
- Osteoporosis prevention/treatment: the longer you treat the better
- Cognition: Other than in premature menopause (natural or surgical) where its helpful, some data says NO benefit and NO harm, whereas other data suggests harm, and there is data that implies there is benefit - UNCLEAR

So, what's the dilemma?

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The Challenge of Safe, Effective HRT

Low Estrogen (E)

- Cardiovascular Disease
- Osteoporosis
- Vaginal Atrophy, Incontinence
- Cognitive Decline
- Poor Quality of Life

High E, Low P

- Breast Cancer
- Endometrial Cancer

How do we minimize these risks without increasing these?

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Citations (2005-2015)

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- Luine VA. Estradiol and cognitive function: Past, present and future. *Horm Behav*. 2014; 66: 602-618
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- Sullivan SD, et al. Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. *Fertil Steril*. 2016; 106(7): 1588-1599
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- Morgan KN, et al. Cognitive Changes with Reproductive Aging, Perimenopause, and Menopause. *Obstet Gynecol Clin North Am*. 2018; 45(4): 751-763

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The Major Risk Associated with HRT

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Breast Cancer and HRT

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Breast Cancer and HRT: Contraindications

Undiagnosed abnormal genital bleeding
Known, suspected, or history of cancer of the breast
Known or suspected estrogen-dependent neoplasia including endometrial cancer
Active DVT, pulmonary, embolism, or history of these conditions.
Active arterial thromboembolic disease (for example, stroke, MI) or a history of these conditions.
Known anaphylactic reaction or angioedema in response to any ingredient in the medication
Known liver impairment or disease
Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders
Known or suspected pregnancy

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Breast Cancer and HRT: Risk Factors

Non-Genomic Risk Factors

- Increased BMI/Obesity
- High Insulin/IGF-1
- High estrogen exposure
- High baseline estrogen
- Dense breasts
- Parity
- Abnormal estrogen detoxification and methylation
- Exposure to toxins

Genomic Risk Factors

- Strong family history
- Detoxification/metabolism SNP's
- Breast cancer risk genetics
  - Ie –BRCA 1/2

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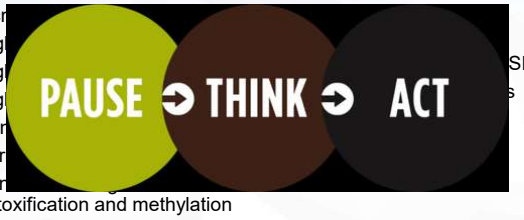
Breast Cancer and HRT: Risk Factors

Non-Genomic Risk Factors

- Incr
- Hig
- Hig
- Hig
- Der
- Par
- Abn detoxification and methylation
- Exposure to toxins

Genomic Risk Factors



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Minimizing HRT Risk Factors

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Who? When? How Long To Treat?

- For women < 60, and/or within 10 years of natural menopause, hormone replacement therapy (HRT) **benefits outweigh the risks**
- In older women (> 60), and/or women > 10 years past menopause, HRT's **risk-benefit balance is less favorable**, particularly with regard to cardiovascular risk and cognitive impairment. **Careful consideration is necessary** regarding HRT risks vs its benefits

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Minimizing HRT Risks: How Long To Treat

- For women with premature menopause (<40) or premature surgical menopause, HRT's benefits generally outweigh the risks. HRT should be continued until natural menopause age (~ 52)
- The combined HRT duration is ideally limited to **< 5 years** (unless premature menopause) because of the known **increase** in **breast** and **endometrial cancer risks after 5 years** of use

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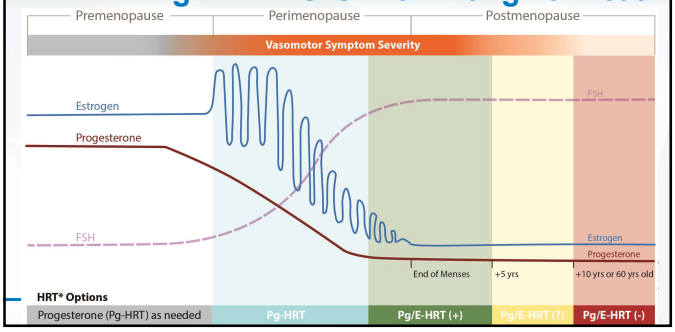
Minimizing HRT Risks: How Long To Treat



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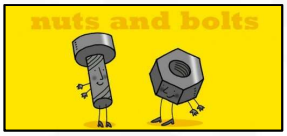
72

HRT: How to do it

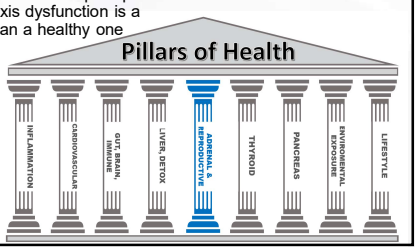


HRT

73

HRT: The Do's

- Optimize the "Pillars of Health"
  - An inflamed, overweight woman with poor phase I/II metabolism and HPA axis dysfunction is a very different candidate than a healthy one



74

HRT: The Do's

- Optimize the "Pillars of Health"
- Determine if HRT appropriate
  - Mammography results
  - Gyn considerations
- Test, don't guess
  - Measure levels and metabolites before giving hormones
- Choose the hormone(s)
  - E2? Pg? T? DHEA?

75

HRT: The Do's

- Optimize the "Pillars of Health"
- Determine if HRT appropriate
  - Mammography results
  - Gyn considerations
- Test, don't guess
- Choose the hormone(s)
- Select the carrier and route of administration (ROA)
- Decide the dosage(s)
  - Depend on ROA and baseline levels
- Monitor outcome
  - Symptom relief
  - Hormones and metabolism
  - Breast exam + mammography
  - Pelvic if appropriate

Start low, go slow and maintain lowest possible dose for symptom relief and safety

76

HRT: Some Debates are Settled

- **Oral bioidentical E2 is effective but transdermal E2 is preferred**

77

Transdermal Estradiol (TDE) vs Oral

- TDE is as efficacious as oral estrogens
  - TDE provides **equal VMS relief** as oral estrogen
  - TDE **maintains and improves BMD** as well as oral estrogens
    - However, there have been no clinical trials assessing TDE's effectiveness on fracture risk
    - TDE dose as low as 0.014mg/day when compared to placebo, over 2 years increased BMD
  - Both TDE and oral E's **improve lipid profiles**
    - Oral: ↑HDL, ↑TG, ↓LDL
    - TDE: ↓TG, neutral effect on HDL, neutral effect on LDL number
      - Increases LDL particle size thereby making more resistant to oxidative damage
  - TDE **provides similar** CVD and cognitive (?) protective effects

78

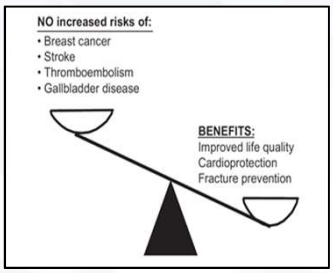
Transdermal Estradiol (TDE) vs Oral

- TDE is safer than oral estrogens. TDE does not
  - Increase clotting factors: DVT and/or PE
  - Increase stroke risk or Blood pressure
  - Have hepatic or GI "first pass" metabolism effects: No increase in
    - CRP and MMP-9
    - Binding proteins: SHBG, TBG, CBG
      - Oral E's increase these binding proteins, decreasing free hormones: T, T3/T4, cortisol
  - Decrease IGF-1
- TDE requires lower doses, maintains stable serum levels

Bottom line: TDE is safer and as effective, maybe even more so, than any oral estrogen

79

Transdermal E2: Summary



Adapted from: L'Hermite M. *Climacteric.* 2017; 20(4): 331-338

80

HRT: Some Debates are Settled

- Oral bioidentical E2 is effective but transdermal E2 is preferred
- **Bioidentical hormones are preferred compared to Premarin and/or synthetic progestins**

81

Bioidentical Hormones: The Best Choice

- Bioidentical hormones are compounds that have exactly the same chemical and molecular structure as endogenously produced hormones
- There are FDA approved bioidentical hormones for E2, P, T
- There are no FDA approved E3 options
- HRT success can be achieved with products that are not FDA approved

82

Bioidentical Hormones: The Best Choice

- Reasons to use compounded hormones (not FDA approved)
  - Peanut allergy – can't use Prometrium
  - Patient's may be sensitive to carrier – so can choose
  - Prefer to use vaginal estriol
  - If necessary, able to change the hormone ratios to optimize HRT
- If choose to use, document as to why NOT choosing an FDA approved available option
- Know your compounding pharmacist – not all compounding is the same

83

HRT: Some Debates are Settled

- Oral bioidentical E2 is effective but transdermal E2 is preferred
- Bioidentical hormones are preferred compared to Premarin and/or synthetic progestins
- When ERT is given to a woman with a uterus, progesterone must be given – oral MP (200mg) is proven to effectively balance ERT
- Saliva testing should not be used to monitor transdermal hormones

84

Commonly Used FDA Approved HRT Products

FDA Approved Product	Dose Proven to be Effective
• Oral progesterone	• 200mg given continuously
• Transdermal E2 patch	• 0.014-0.1 (0.05 most common)
• Transdermal E2 gel	• 0.25mg and higher

Start low, go slow and maintain lowest possible dose for symptom relief and safety

85

Progesterone: General Information

- Progesterone inhibits estrogen-stimulated breast epithelial cells
- Progesterone down-regulates estrogen receptor-1 (ER1) in the breast
- Progesterone induces breast cancer cell apoptosis
- Progesterone exhibits anti-hypertensive activity
- Progesterone is lightly sedating
  - Improves falling asleep
  - May restore disrupted sleep

86

Progesterone and the Endometrium

- Oral micronized progesterone (200mg/day) offers the best endometrial protection when used for up to 5 years
  - French observational studies: E3N, EPIC
  - US: Randomized, double-blind, placebo-controlled trials: KEEPS, ELITE

87

Progesterone: Cyclic or Continuous

- Continuous rather than cyclic progesterone is the best protection against endometrial hyperplasia and carcinoma

- **Bottom Line: Only a continuous progesterone regimen should be used for complete endometrial protection**

88

Progesterone: Cyclic or Continuous

- Continuous rather than cyclic progesterone is the best protection against endometrial hyperplasia and carcinoma
  - UK study (2000): open prospective study to determine the endometrial hyperplasia prevalence in women taking sequential HRT and in women using a continuous HRT regimen for 9 months
    - Results: A continuous regimen converted the endometrium to normal in women who developed hyperplasia, including complex hyperplasia while on a sequential regimen
  - EPIC (2010): French observational study report increased endometrial cancer risk in all combined sequential regimens
    - Continuous regimens superior to sequential regimens for endometrial protection
- **Bottom Line: Only a continuous progesterone regimen should be used for complete endometrial protection**

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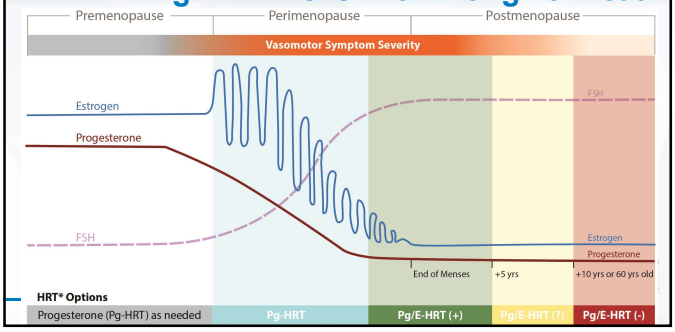
Progesterone and the Breast

- Estrogen (preferably transdermal patch) combined with oral micronized progesterone (200mg/day) does not increase breast cancer risk for up to 5 years
  - After 5 years there is a small increased breast cancer risk
- Estrogen (preferably transdermal patch 0.025mg) combined with vaginal micronized progesterone(100mg/day) does not increase breast cancer risk for up to 5 years
  - ELITE: 17β-estradiol and vaginal micronized progesterone 45mg (gel)
  - **There are very few epidemiologic studies available assessing vaginal progesterone and breast cancer – NOT recommended**

90

Minimizing HRT Risks: How Long To Treat



91

Transdermal Progesterone

Women with a uterus: NEVER

Women without a uterus: You decide!
Very few studies, relieves VMS, dose dependent

92

TDE + MP: Summary

- Safest and possibly most effective regimen: **transdermal estradiol + oral micronized progesterone**
  - TDE is the safest and probably most effective estrogen for VMS relief
- A **continuous progesterone regimen provides the most complete endometrial protection**
- Vaginal progesterone may be effective – minimal evidence
- **Never use transdermal progesterone in a women on ERT with a uterus**

93

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98

HRT: Other FDA Approved Options I use

- Vaginal progesterone
- Vaginal DHEA

HRT: Non-FDA Approved Options I use

- Vaginal E3 cream
- Transdermal E3 cream
- Testosterone cream

99

Vaginal Progesterone

- Vaginal micronized progesterone (100mg/day) may offer endometrial protection when used with a low dose transdermal estradiol patch (0.025mg/day) for 3-5 years – off label
  - ELITE: 17β-estradiol and vaginal micronized progesterone 45mg (gel)
  - **There are very few epidemiologic studies available assessing vaginal progesterone and endometrial protection – NOT recommended without endometrial surveillance**

100

We Skipped One of These

Low Estrogen (E)

- Cardiovascular Disease
- Osteoporosis
- Cognitive Decline
- **Vaginal Atrophy, Incontinence**
- Poor Quality of Life

High E, Low P

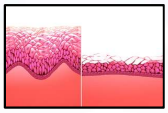
- Breast Cancer
- Endometrial Cancer

How do we minimize these risks without increasing these?

101

Comorbidities of Low Estrogen

- Cardiovascular Disease
- Osteoporosis
- Cognitive Decline
- **GSM (Genitourinary Syndrome of Menopause)**
  - Vaginal atrophy, incontinence
  - Vaginal dryness, itching, dyspareunia



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HRT and GSM

- GSM is defined as signs and **bothersome** symptoms associated with estrogen deficiency involving labial, introital, clitoral, vaginal, urethral, and bladder changes
- Vulvovaginal atrophy is highly prevalent, especially as women get older
  - It can occur in up to 84% of women
- Symptoms include
  - Genital irritation, dryness, and burning
  - Urinary urgency, dysuria, and recurrent UTIs
  - Sexual symptoms of pain and dryness, leading to decreased libido

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HRT and GSM

- Physical exam findings include
  - Labial thinning, narrowing of the introitus, and decreased width and depth of the vagina
  - Vulvar and vaginal tissues may be pale and dry with loss of rugae and elasticity
  - Mucosal inflammation is common with erythema and friability
  - Findings may be mild, moderate, or severe
- Laboratory testing not necessary, but findings include
  - ↑vaginal pH, loss of superficial cells, ↑parabasal cells

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HRT and GSM: Non-Hormonal Tx

- Vaginal lubricants and moisturizers
  - Natural oils (including olive, mineral, or coconut) are a simple, inexpensive option for both sexual activity and regular moisturizing
    - Not with a condom
    - Natural oils have not been well-studied
  - Water based lubricants-provide both moisture and slip
  - They should be applied to the vulva and vagina regularly, typically every 1 to 3 days, depending on symptom severity and atrophy
- Vaginal lubricants and moisturizers also may alter the vaginal microbiome, increasing the risk of vaginal infection or discharge

105

HRT and GSM: Non-Hormonal Tx

- Sexual/vaginal activity on a regular basis
  - With a partner
  - Without a partner
- Pelvic floor physical therapy (PT)
- Vaginal dilator therapy
  - Performed independently
  - Performed under the guidance of a professional
- For women with insertional dyspareunia, another nonhormonal option is topical lidocaine: 4% lidocaine applied to the vulvar vestibule prior to intercourse

106

GSM Tx: Vaginal Estradiol (E2)

- FDA approved bioidentical vaginal estradiol does exist
- Not the first choice to treat the GSM
  - **The risks of endometrial hyperplasia and cancer have not been thoroughly evaluated, especially in the long term**
- An option when other non-hormonal therapies fail
  - Vaginal lubricants or moisturizers, vaginal activity
- Whenever you use vaginal E2 – MUST make sure levels are in the postmenopausal range if you want to avoid systemic E2
- **Before considering: rule out endometrial pathology**

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GSM Tx: Vaginal E2

- Vaginal cream: Estrace: 0.1mg/gm active 17β-estradiol
  - 1-4g/day for 1-2 weeks, then 0.5-1.0 gram 1-3x/week
- Vaginal ring: Estring: a 2mg ring
  - Releasing ~ 7.5mcg/d x 90 days
- Vaginal tablets: Vagifem: 10mcg tab
  - 1 tab daily x 2 weeks, then 1 tab 1-3x/week
- Data documents low systemic absorption with ring and tablet
- **Use lowest dose that relieves symptoms**

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GSM: Estriol (E3): General Information

- A final metabolite in estrogen synthesis, weakest estrogen
  - 95% excreted in urine as a glucuronide
- Binds ERβ: ERα in a 3:1 ratio
- **Not FDA approved – compounded only**
- Theoretically, better safety profile for breast health
- Provides symptomatic relief
- No data on transdermal E3's health benefits
- There is data on vaginal E3's QOL benefits

109

GSM Tx: Vaginal E3

- **Must exclude endometrial pathology prior to vaginal E3**
- Outside of the US, studies show that for GSM
  - Daily low-dose-vaginal estriol (0.05mg) is safe and effective
    - No increased risk of endometrial pathology
  - Daily ultra-low-dose vaginal estriol (0.03mg) is safe and effective
    - No endometrial effect
    - Does not increase systemic E1/E2 levels
    - No endometrial proliferation, therefore does not require opposing progesterone
    - No adverse effects
- **Outside the US effective vaginal estriol doses ranging from 0.02mg to 0.05mg and are safe and effective**

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GSM Tx: Vaginal E3

- Within the US, compounded vaginal estriol
  - Dose: 1mg/gm apply 1gm nightly x 2-3 weeks, then 1-3 x/week
  - Doses as low as: 0.5mg can be effective
  - Place in a non-toxic base: versa base or mucolox base
- Lower one-third of the vagina is hormonally responsive
  - Apply to lower one-third of the vagina for best results
- Does not require concomitant progesterone
- Compared to vaginal E2, E3 is probably safer because
  - E3 is short acting, has a low affinity for the estrogen receptor, has a short receptor occupancy, and binds 3:1 ERβ to ERα

111

GSM Tx: Vaginal DHEA

- Vaginal DHEA is FDA approved
  - **Intrarosa: 6.5mg vaginal suppository daily at bedtime**
- Vaginal DHEA does improve vulvovaginal atrophy symptoms
  - Dryness, itching, dyspareunia
- Vaginal DHEA does not
  - Increase systemic sex hormone levels – are inactivated prior to release into circulation then eliminated by kidney and liver
  - Lead to endometrial thickening/hyperplasia
- **Bottom Line: benefits > risks**

112

GSM Tx: Vaginal DHEA

- Though FDA approved, only evaluated in postmenopausal women (natural and surgical) NOT on other HRT
- So, the efficacy and risk factor profile in women also using a transdermal estrogen patch + oral micronized progesterone is unknown
- However, given it does not effect systemic estrogen/androgen levels, it should be okay – but be cautious
  - **Doses >6.5mg may increase systemic levels of DHEA, T, etc.**
- Additionally, there are no long term studies to asses long-term safety, on Intrarosa with or without concomitant HRT

113

Citations

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118

HRT: Other FDA Approved Options I use

- Vaginal progesterone
- Vaginal DHEA

HRT: Non-FDA Approved Options I use

- Vaginal E3 cream
- Transdermal E3 cream
- **Testosterone cream**

119

Testosterone: General Information

- Testosterone (T) is the most abundant female hormone
- Maximum concentrations occur during the 3rd and 4th decades, then slowly decline
- Androgen receptors (AR) are virtually in every tissue and organ system, including the breast
- T and its active metabolite, DHT have a direct physiologic effect at the AR
- T is the precursor hormone for E2 and has an indirect effect on the ER via aromatization

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Testosterone: General Information

- **Physiologic** T levels are critical for overall mental and physical health, immune, glycemic control, and reducing inflammation, ALL of which impact cancer risk
- Circulates bound to SHBG and albumin – biologically active T is impacted by factors altering SHBG levels, including obesity and estrogens
- Testosterone replacement therapy (TRT) may improve sexual function, quality of life, mood, and bone density
- TRT side effects include: acne, hirsutism and is dose dependent

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Testosterone: The Data

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Testosterone: The Data

- Exogenous testosterone is not FDA approved for women
- In the US, TRT may be compounded as a cream, gel, or pellet
- TRT and cardiovascular risk
  - There are no long-term prospective studies sufficiently powered to assess CV risk associated with T therapy in women
- TRT and endometrial hyperplasia/cancer risk
  - Available evidence does not support an increased endometrial cancer risk with transdermal or pellet therapy
  - However, oral T increased endometrial hyperplasia

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Testosterone: The Data

- TRT and breast cancer risk
  - **No randomized data investigating breast cancer risk with T** replacement as a primary outcome
  - Epidemiological studies linking elevated androgen levels to breast cancer produced conflicting results
    - Androgens inhibit estrogenic effects on mammary growth, T may reduce adverse estrogen effects on breast tissue
    - Observational trials – high androgen levels increase BC risk
  - However, PCOS patients (high androgens) and female-male transgender patients who receive high T doses do not have an increased BC risk
  - Data on BC and transdermal/pellet therapy no increase in breast cancer

124

Testosterone: The Data

However, there is no evidence that the addition of TT to TDE + oral MP increases breast cancer risk!

125

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128

A Case

How to address Estrogen Sensitive Issues

129

51 y/o woman with symptomatic fibroids and strong family hx of breast cancer. Wants HELP!

- 51 yo P0 LMP 3 weeks ago wants to decrease her risk of breast cancer. She is concerned because her mother was recently diagnosed with early stage BrCa at age 78 and she is seeing this in her friend group as well as in her extended family. Ashkenazi Jewish.
- PMH:
  - Fibroids and heavy bleeding x 4 years
  - Borderline blood sugars x last few years.
  - Been told she needs to lose weight
  - Dense Breasts on Mammogram (last mammo 2 months ago)
  - BRCA test NEG
  - Cardio CRP 4.6

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- ROS:
  - BM 3x per week
  - Occasionally has intermittent diarrhea and gas shortly after eating
  - Joint aches, especially knees
  - Under a lot of stress: Finances, Marriage, Children going to College
- PE and labs:
  - BMI 25 , BP 135/85
  - Fasting Glu 105, Fasting Insulin 18
  - Hgb 9, HCT 28

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What we know:

- She has a strong FH of breast cancer.
- She is overweight.
- She has insulin resistance.
- She is estrogen dominant due to her dense breasts, fibroids and heavy periods
- She is inflamed from her elevated Cardio CRP and knee pain
- Her gut is out of balance and inflamed from her constipation alternating with pain and diarrhea.
- She is under stress.
- She is anemic from her heavy bleeding.

132

What we now know: She is at increased risk of Breast Cancer because:

- She has a strong **FH** of breast cancer.
- She is **overweight**.
- She has **insulin resistance**.
- She is **estrogen dominant** due to her **dense breasts**, **fibroids** and heavy periods
- She is **inflamed** from her **elevated Cardio CRP** and knee pain
- Her **gut is out of balance and inflamed** from her **constipation** alternating with pain and diarrhea.
- She is under **stress**.

133

- These are estrogen dominant concerns, so framework is to decrease estrogen intake and formation and increase estrogen elimination.

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- That means:
  - Organic, whole foods w/o hormones or xenoestrogens
  - Flax seed which doubles as fiber and aromatase inhibitor
  - Probiotic and healthy gut to decrease beta glucuronidase
  - Eliminate constipation with Mg, Aloe or additional fiber if Flax isn't enough
  - Natural aromatase inhibitor's like green tea
  - Detox nutrients (refer to detox module)
  - Check for Detox SNP's (methylation and estrogen metab) and adjust diet and supps as needed

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More nutritional Recommendations:

- Eat the rainbow every day
- No refined sugar
- Cruciferous Vegetables
- Herbs and Spices (ginger and Turmeric)
- Green Tea
- Organic, non-GMO Soy
- Reduced Caloric Intake
- www.keep-a-breast.org

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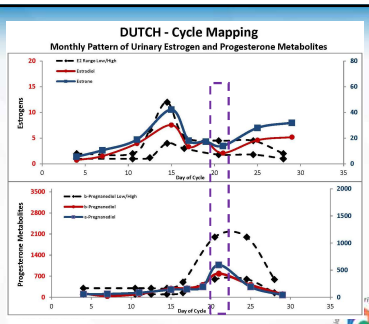
Cycle Map

- DUTCH Complete estrogen and progesterone metabolite data is taken from the day with the Pg peak
- Day 21 has normal E2 but E2 is very high later in her cycle



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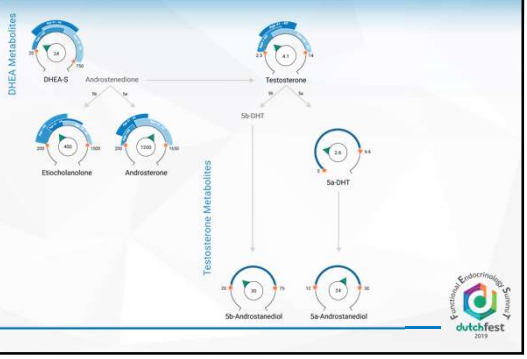

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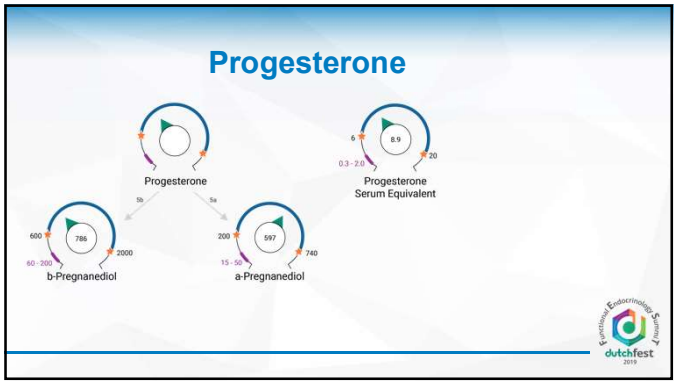

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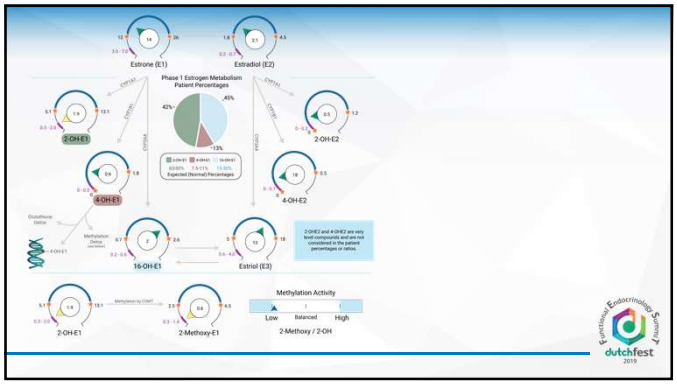

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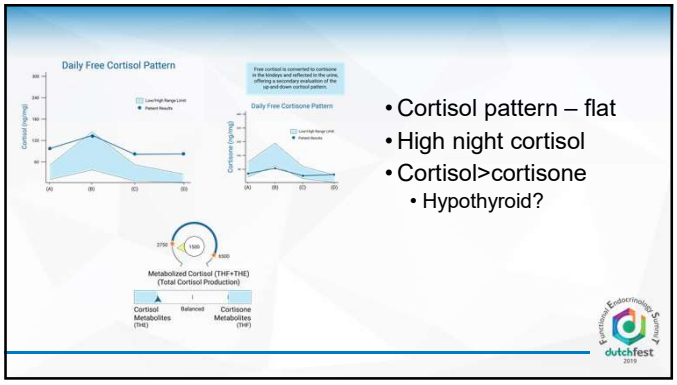

- Cortisol pattern – flat
- High night cortisol
- Cortisol>cortisone
  - Hypothyroid?

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More things to do:

- Reduce inflammation (PGE2 stimulates aromatase)
- Reduce stress (Stress is pro-inflammatory)
- Normalize body weight (Obesity reduces SHBG and leads to more free Estrogen)
- Normalize blood sugar and insulin (Insulin lowers SHBG) with LGI Diet
- Iron rich foods
- Elimination Diet or Food Sensitivity Testing to Identify Dietary Sources of Inflammation.
- ***TEST FOR E and E METAB AND NORMALIZE***

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