



# Menopause Transition and Hormone Therapy

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# Objectives

- Understanding the physiology of menopause transition
- Benefits and contraindications of hormone therapy
- When to transition from contraception to menopause therapy
- Oral vs transdermal vs vaginal hormone therapy

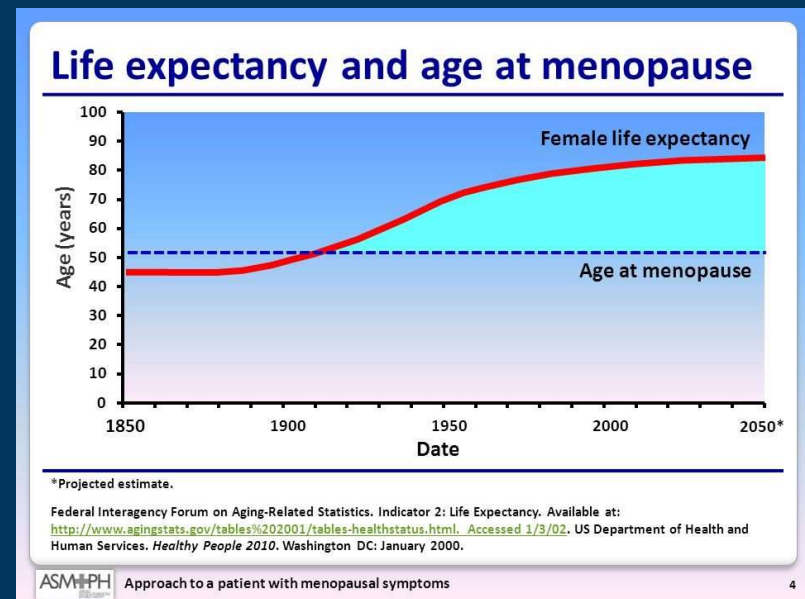
# Introduction

## Menopause

- A normal, natural event, defined by the final menstrual period (FMP) and confirmed after 1 year of no menstrual bleeding.
- Represents the permanent cessation of menses resulting from loss of ovarian follicular function, usually because of aging.
- Normally occurs between the ages of 40 and 58 years.

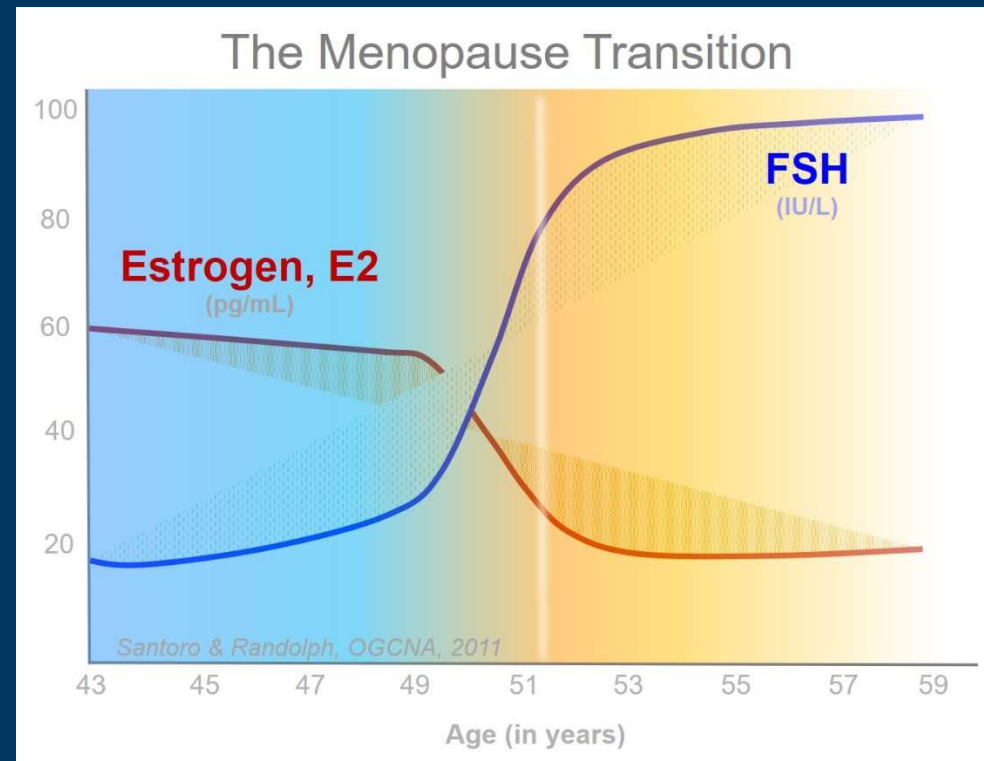
## Women worldwide are living longer

- Many women will spend nearly 40% of their lives in postmenopause.
- More than 60% survive at least until aged 80 years

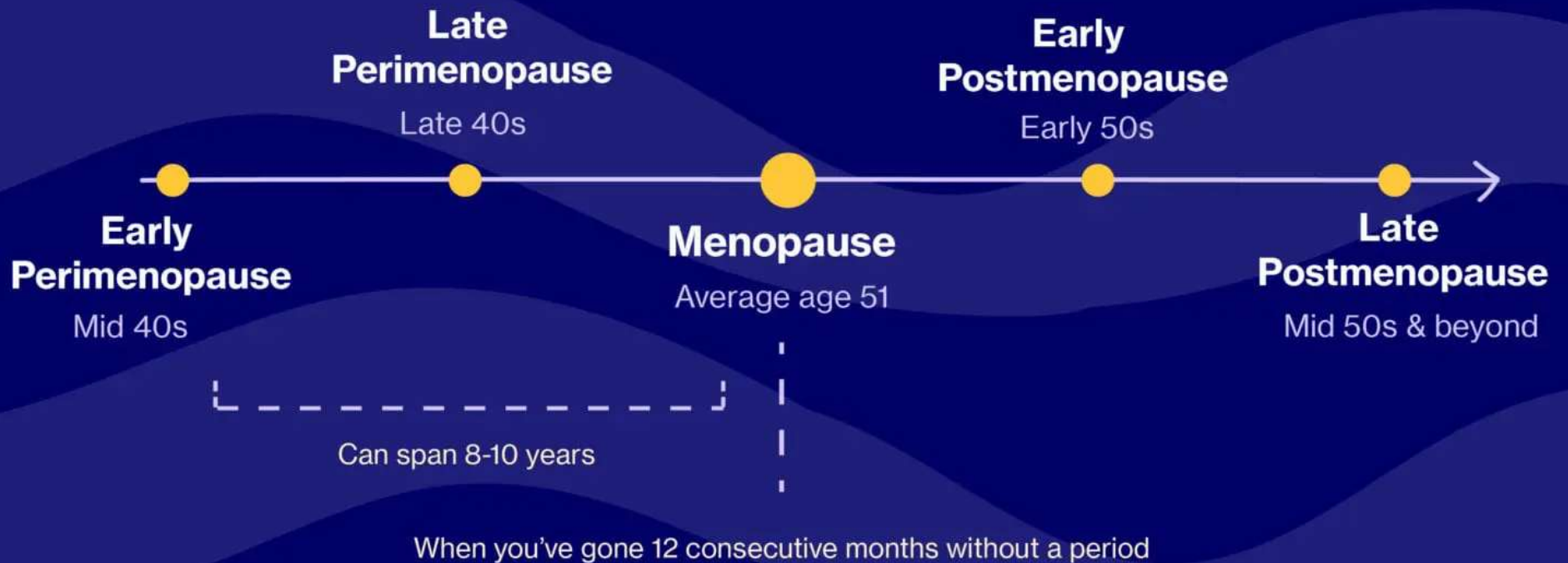


# Menopause Transition (Perimenopause)

- Most symptomatic time in the continuum from pre-menopause to post menopause
  - Abnormal Uterine Bleeding
  - Vasomotor Symptoms(VMS)
  - Increased premenstrual syndrome (PMS)
  - Sleep disruption
  - Irritability/Mood Changes
  - Weight Changes
  - Cognitive Changes
  - Skin and Hair Changes
  - And many more....



# Stages of the Menopause Transition



## Early Menopause Transition

- Persistent cycle irregularity by  $\geq 7$  d.
- Decline in inhibin B and Anti-Mullerian Hormone (AMH) because of reduction in follicles: low antral follicle count (AFC).
- Diminished ovarian reserve. Lower AMH and inhibin B promotes growth of remaining follicular pool, accelerating follicular atresia.
- Early follicular FSH is variable.
- May or may not have mild vasomotor symptoms (VMS).
- May have pronounced premenstrual syndrome.

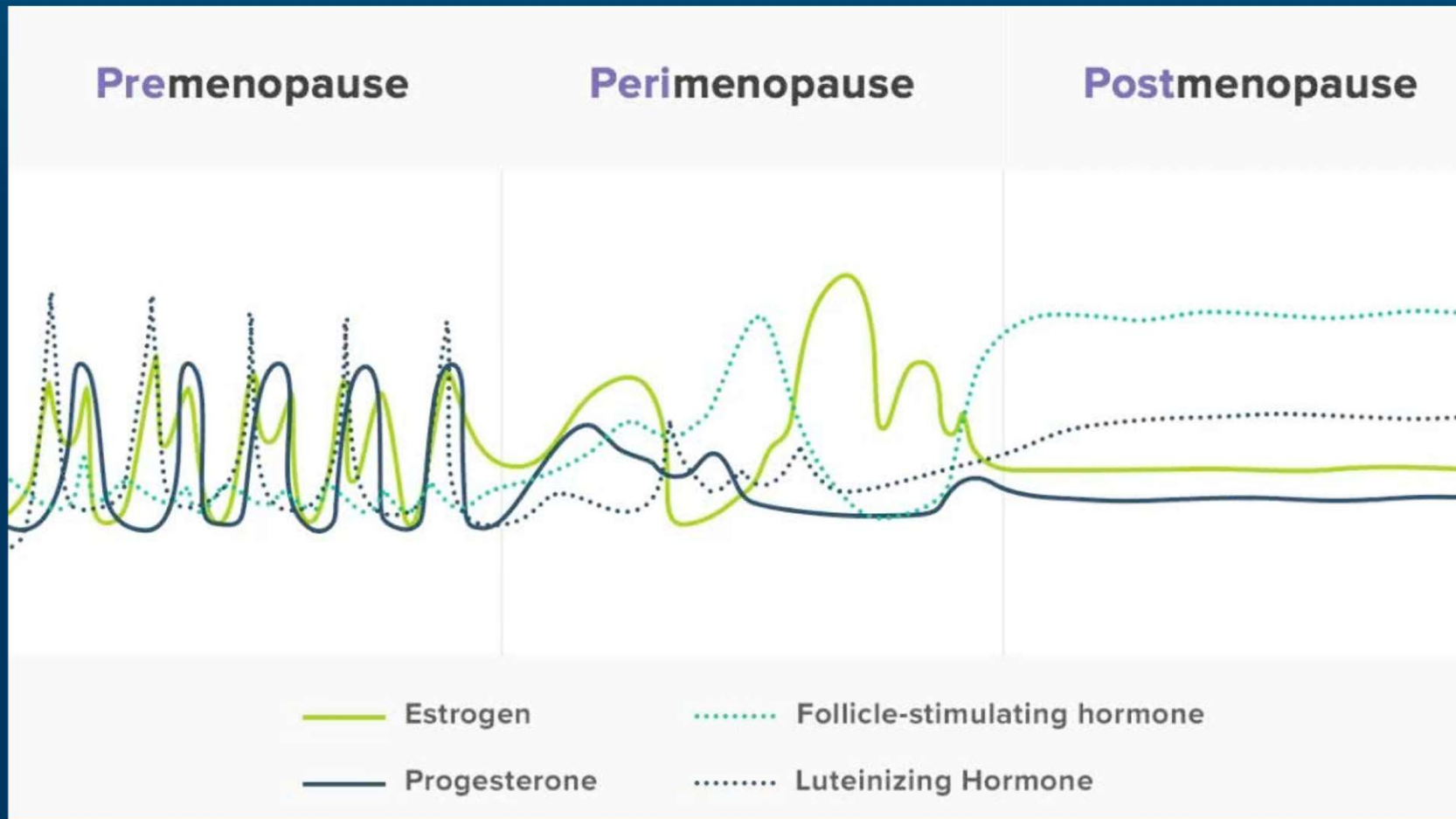
## Late Menopause Transition

- Amenorrhea  $> 60$  d.
- Menstrual cycles have variable cycle length.
- Variable estradiol levels with increased prevalence of anovulation.
- FSH levels are  $\geq 25$  IU/L because of few remaining oocytes.
- Negligible AMH and AFC.
- VMS and other signs of menopause likely.

Hale GE, et al. *Menopause* 2009;16:50-59. doi: 10.1097/GME.0b013e31817ee0c2; Harlow SD, et al. *Menopause* 2012;19:387-395. doi: 10.1097/gme.0b013e31824d8f40; Santoro N, et al. *J Clin Endocrinol Metab* 2008;93:1711-1721. doi: 10.1210/jc.2007-2165; Soules MR, et al. *Menopause* 2001;8:402-407. doi: 10.1097/00042192-200111000-00004

# Hormones During Perimenopause





From [womenlivingbetter.org](http://womenlivingbetter.org) adapted from:  
Santoro N, Brown JR, Adel T, Skurnick JH. Characterization of reproductive hormonal dynamics in the perimenopause. *J Clin Endocrinol Metab.* 1996 Apr;81(4):1495-501. doi: 10.1210/jcem.81.4.8636357. PMID: 8636357. 8

# Evaluation: Take Home Points

- Laboratory testing for hormone levels is NOT helpful in majority of cases
  - Rule out other causes of the symptoms like anemia, thyroid dysfunction

# Perimenopause Hormone Therapy

- Goal is to take away the high and lows of the hormonal swings
- HT is frequently too low of a dose to control the cycles and will result in bleeding
- **Need to consider need for contraception**
- Continuous combination oral contraceptive (COC)
- IUD with estradiol
- Drospirinone oral contraceptive with estradiol

How long should we continue perimenopause therapy?

Do we really need HT after perimenopause?

What about risk of breast cancer?

# Hormone Therapy(HT)

- Benefits of HT
- Transitioning from contraception to HT
- Contraindications of HT
- Vaginal therapy

# Categories of Hormone Therapy

## Estrogen therapy (ET)

- Unopposed systemic estrogen for postmenopausal women who have undergone hysterectomy or vaginally in low doses for women with vaginal symptoms regardless of presence of uterus.

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## Estrogen-progestogen systemic therapy (EPT)

- For postmenopausal women with a uterus.
- Progestogen reduces the risk of endometrial adenocarcinoma because of unopposed estrogen.

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## Progesterone systemic therapy (PT)—off-label

- In those with VMS with contraindications to ET.

## FDA Indications for HT

- VMS, including hot flashes and night sweats.
- Prevention (not treatment) of bone loss or osteoporosis.
- Treatment of premature hypoestrogenism because of
  - Hypogonadism
  - Bilateral oophorectomy
  - Primary Ovarian Insufficiency
- Genito-urinary Syndrome of Menopause (GSM).

## But...what else can it do

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May be cardioprotective, especially if started within 5\* years of final menstrual period(FMP)

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Impact lipids

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Decrease risk of T2DM

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Brain health

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Can help with libido

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Increases quality of life

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Helps with arthralgia

## But...is it safe

### Breast cancer

- WHI used conjugated equine estrogens (CEE) and medroxyprogesterone (MPA)
- Unusually low risk in control group of breast cancer in CEE-MPA arm
- 0.9 additional cases of breast cancer per 1000 woman years and no increase in breast cancer deaths
- E alone likely lowers risk
- Observational studies looking at micronized progesterone (prometrium) seem to show less impact

### VTE

- Oral vs transdermal

# When to Transition

- Individualization is required.
- May continue contraception until typical age of menopause (51-52 y) or when 90% of women reach menopause (55 y).
- Can transition from hormone contraception to HT if still symptomatic.
- Hot flashes may reappear transiently because birth control has higher hormone concentrations than HT.



# Timing of HT Initiation

- Timing hypothesis.
  - Less CVD risk associated with HT use and potential CHD and cognitive benefit if initiated closer to the time of menopause.
  - In contrast, HT use initiated further from menopause may be harmful.
- Evidence from the WHI.
  - Absolute risk of CHD was lower in younger, recently postmenopausal women.
  - Use of HT within 10 years of the onset of menopause was associated with a lower CHD risk than if it was started  $\geq 10$  years from the FMP.
  - Women aged 50 to 59 y in the ET arm had a more favorable all-cause mortality outcome and fewer MIs.
- Early Estrogen Prevention Study and the Early Versus Late Intervention Trial With Estradiol suggested cardiovascular (CV) safety of HT initiated early in menopause based on favorable CV biomarkers; underpowered to assess primary CV outcomes.

## Contraindications to Hormone Therapy

Unexplained vaginal bleeding

Prior estrogen-sensitive cancers (breast/ovarian/endometrial)

Triple-negative breast cancer; however, use of HT in symptomatic individuals may be considered if 5 years from diagnosis and treatment has been completed

History of coronary artery disease, stroke, myocardial infarction (MI)

Peanut Allergy (Prometrium)

History of or inherited high risk for VTE

Severe active liver disease

## Non-Hormonal Options

- Vasomotor Symptoms (VMS)
  - SSRI,SNRI, Gabapentin, Oxybutynin, Fezolinetant
- Libido
  - Filbanserin, Bremelanotide
- Hair loss
  - Minoxidil, spironolactone
- Bones
  - Bisphosphonates, Teriparatide

# Oral Vs Transdermal Estrogen Therapy

- Historically, the most widely used form in North America.
- Because of first-pass uptake in the gastrointestinal tract and hepatic metabolism
  - Increase in high-density lipoprotein cholesterol.
  - Associated with 25% increase in triglycerides.
  - Increase in some hepatic globulins, coagulation factors, and inflammatory factors.
  - Decrease in e-selectin, an endothelial adhesion molecule, which may affect coronary artery disease.
  - Increase in sex hormone-binding globulin (SHBG).
- Not subjected to first-pass hepatic metabolism.
- Associated with more stable serum levels.
- Minimal effect on SHBG; therefore, less of a negative effect on sexual functioning.
- Risk of skin-to-skin transfer of small amounts.
- Patch, gel, spray, and emulsion forms are available.
- Adequately powered studies show increase in VTE and stroke with oral ET but not transdermal.

## Systemic vs Vaginal

- Systemic Therapy (oral or TD)
  - Need progesterone for endometrial protection.
    - Progesterone not well absorbed through skin
    - Micronized progesterone or progestin
    - LNG IUD (5 years)
  - Risk of VTE
- Vaginal Therapy
  - Mainly used to treat GSM
  - Cream, tablet, insert and rings available. One of the higher dose rings is used for systemic therapy
  - No systemically absorbed.
  - Endometrial protection not needed\*
  - DHEA, Ospemifene (SERM)

# Bioidentical Hormone Therapy

- Hormones that are chemically identical to hormones produced by ovaries during reproductive years, including estrone, estradiol, estriol, progesterone, testosterone, DHEA, and cortisol.
- Bioidentical is a marketing term not recognized by FDA and is often misused by compounding pharmacies who inaccurately market as “natural” and “safer” when there is no evidence to support these claims.
- **The Menopause Society and ACOG have each released position statements against the use of compounded bioidentical hormones and do not endorse serum, saliva, or urine hormone testing to determine dosing.**
- There are FDA-approved, extremely effective, bioidentical hormones that are monitored and regulated for purity and safety.

Bioidenticals: Sorting Myths From Facts [FDA Consumer Update]. January 9, 2008; Compounded Bioidentical Menopausal Hormone Therapy: ACOG Clinical Consensus No. 6. *Obstet Gynecol* 2023;142:1266-1273. doi: 10.1097/AOG.0000000000005395; Simon JA, et al. *Hormone Testing and Bioidentical Hormones*. 2007. [www.menopause.org/docs/default-document-library/pg06monograpah.pdf?sfvrsn=0](http://www.menopause.org/docs/default-document-library/pg06monograpah.pdf?sfvrsn=0). Accessed May 29, 2024; Pinkerton JV. *OBG Management*, 2009;21:42-52. “The 2022 Hormone Therapy Position Statement of The North American Menopause Society” Advisory Panel. *Menopause* 2022;29:767-794. doi: 10.1097/GME.0000000000002028

# Custom-Compounded Hormone Therapy Formulations Pros and Cons

## Pros

- Allows individualized dosing and combination therapy.
- Various modes of administration: subdermal implants (not recommended), sublingual tablets, rectal suppositories, and nasal sprays.
- For those with allergies or intolerance to FDA-approved therapies, can be prepared without binders, fillers, dyes, preservatives, or adhesives.

## Cons

- Not FDA regulated.
- Do not require proof of claim and are not held to the same standard of manufacture.
- Not found to be safer than FDA-approved formulations in clinical trials.
- May even have harms associated with unknown pharmacokinetics (eg, pellets).
- Lack of monitoring of adverse events.
- Often not covered by third-party payers.

## Take Home Points: Hormone Therapy

- Need progesterone if systemic estrogen and had uterus.
- Compounded hormones are not preferred unless allergies or intolerance to FDA approved products.
- Vaginal estrogen can be used for (almost) everyone.

# Questions?

