UT Southwestern Medical Center

Menopause for the Family Practitioner

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Disclosures

No Disclosures

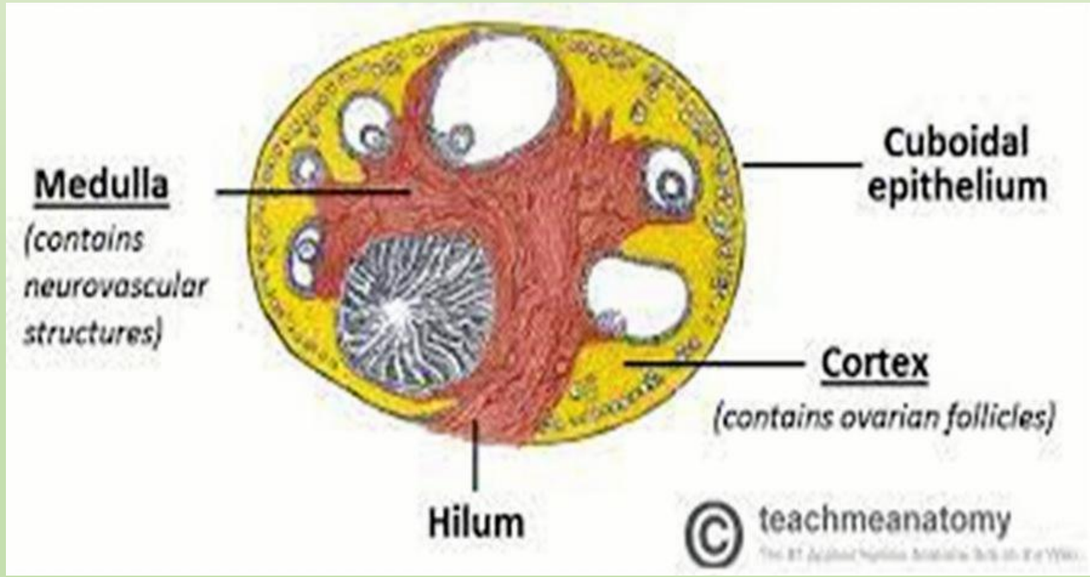
Objectives

- Review the physiology of menopause
- Discuss the clinical symptoms and presentation of menopause
- Describe the evaluation and diagnosis of menopause
- Discuss the treatment options
- Explain the risks/benefits of treatment/no treatment

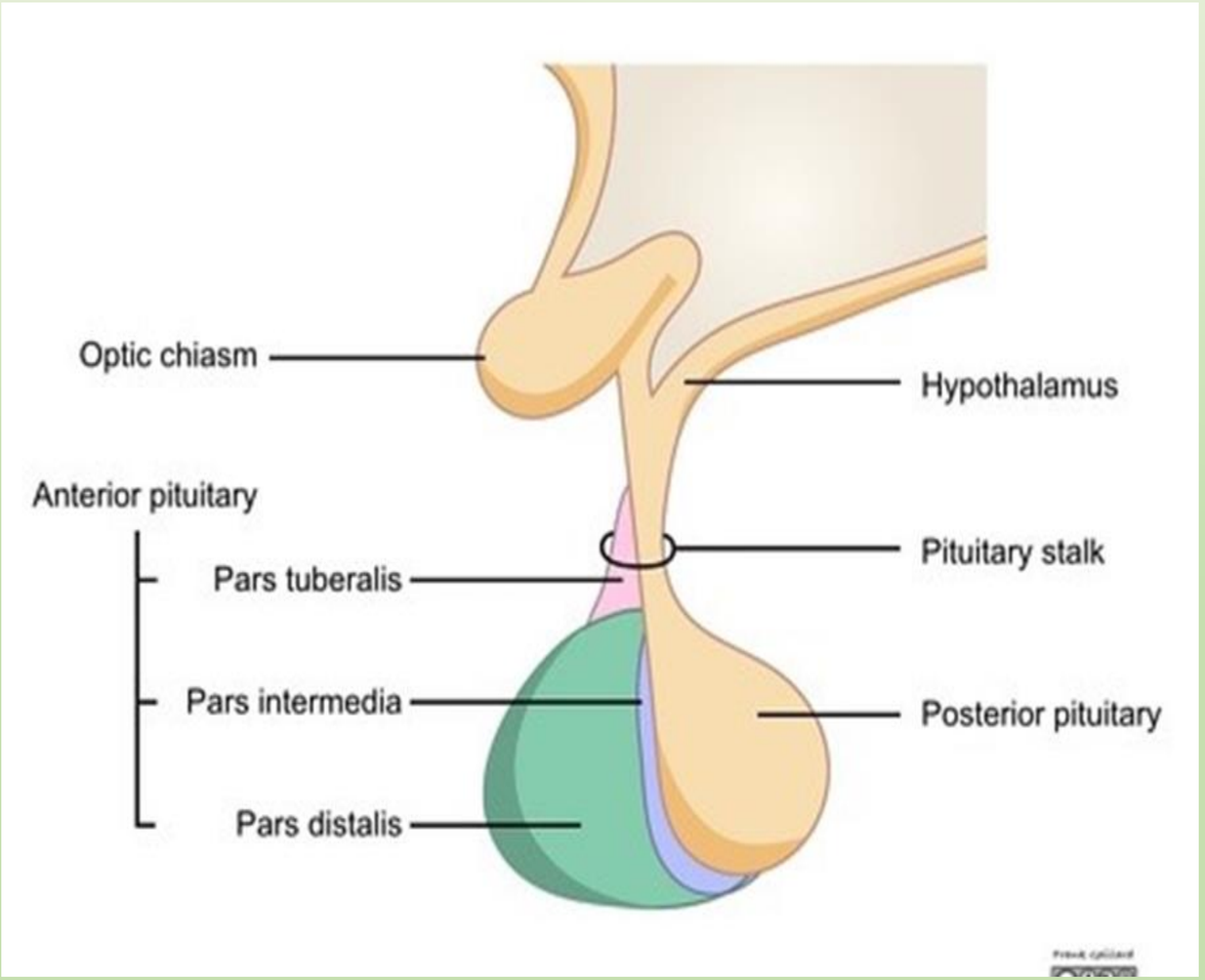
Ovaries

Ova (female gametes)

- Reside in ovarian cortex (outer layer)
- Peak number at 20 weeks gestational age (6-7 million)
- Atresia begins shortly after and for the rest of life
- Approximately 1 million at birth
- 400,00 at puberty
- < 500 ovulate

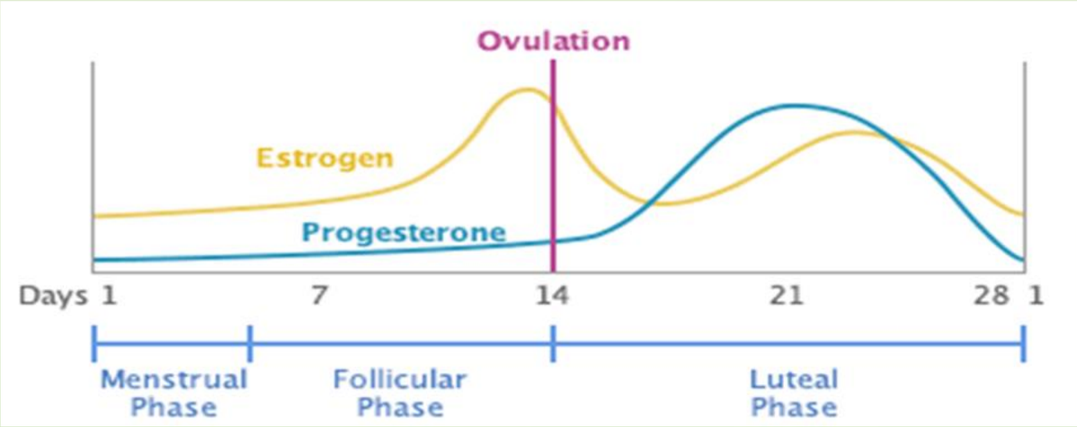


Pituitary Gland



- Produces FSH (follicle stimulating hormone)
- Produces LH (lutenizing hormone)
- FSH drives follicular development
- LH surges midcycle to cause ovulation

Menstrual Cycle



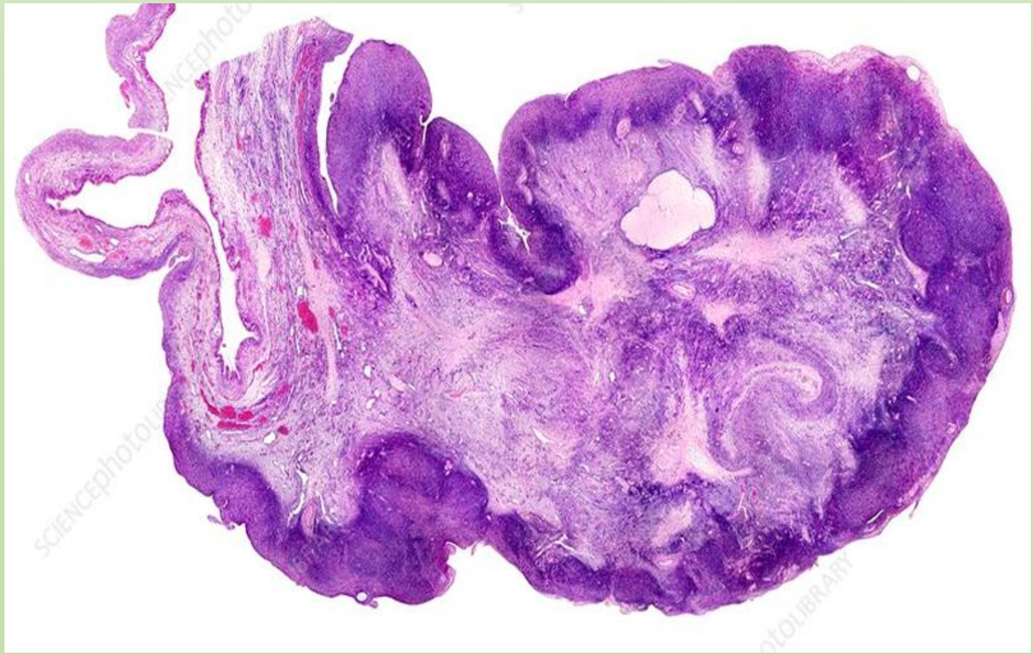
- Multiple ova recruited each cycle under influence of estrogen
- Typically only one becomes “dominant” and ovulates
- The dominant follicle reaches **2-3 cm** during midcycle

- Ovulation occurs after an LH surge
- The corpus luteum develops and produces progesterone
- Progesterone stabilizes the endometrium awaiting implantation
- If implantation does not occur, the endometrium sloughs
- The cycle starts over

End of Reproductive Life

Number of ova diminishes

- ✓ FSH rises as pituitary strives to recruit ova
- ✓ LH rises as pituitary strives to induce ovulation
- ✓ Inhibin levels decrease
- ✓ Antimullerian hormone levels decrease



Definition of the Stages of Life in Women

A group of investigators met in 2001 for the **Stages of Reproductive Aging Workshop (STRAW)** addressing the need for a uniform staging system and definitions for the reproductive years and beyond

STRAW was refined in 2011 to its current staging system

STRAW + 10

First Period							Final Menstrual Period				
Stage	-5	-4	-3b	-3a	-2	-1	0 / +1a	+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	No Period		No Period	No Period	

Perimenopause

Hallmark: “irregular periods”

- Corresponds with STRAW -2 (early) and STRAW -1 (late)
  Early: cycles vary plus or minus 1 week
  Late: cycles extend (skipped periods)
- Estrogen levels are high and fluctuate
- No progesterone production if ovulation does not occur
- May be associated with night sweats and hot flashes
- Often confused with menopause due to similar symptoms but physiology is much different

LOOP Ovulation

- Luteal out of phase (LOOP) event
- Occurs due to a 2nd peak of estrogen in the luteal phase due to prolonged elevations of FSH in the proliferative phase
- Can trigger an LH surge and ovulation sometimes in the early proliferative phase of the next cycle
- Cause of irregular cycles—both shorter (<21 days) and longer (>40 days)

Menopause

Occurs when ovarian reserve is depleted

Average age 50-51 in US

- “Premature” if < 45
- “Primary ovarian insufficiency” < 40

Definition: absence of menses for 12 months

STRAW + 10

	First Period					Final Menstrual Period					
Stage	-5	-4	-3b	-3a	-2	-1	0	+1a	+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*
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Symptoms

Night sweats

- may occur in late 30's and 40's
- not necessarily associated with estrogen deficiency
- Hormone levels can be "normal"

Hot flashes

- occur with drops in fluctuating estrogen levels during perimenopause
- occur due to estrogen deficiency in menopause

Symptoms

- Mood swings and “Brain fog”
- Difficulty sleeping
- Fatigue
- Anxiety/palpitations
- Joint pain
- Vaginal dryness
- Sudden weight gain
- Hair loss
- Loss of muscle mass

Treatment options

- ✓OTC
- ✓Hormonal
- ✓Non-Hormonal

The Hormone Therapy Story

Nurses' Health Study

- Started in 1976
- >120,000 registered nurses
- Periodic questionnaires about lifestyle and health
- Found lower incidence of cardiovascular disease in women on hormone therapy (HT)

Hormone therapy in the 1990's

Premarin: Conjugated Equine Estrogen

Prempro: Premarin *plus* medroxyprogesterone

Estrogen increases endometrial cancer risk in women with a uterus

Addition of progesterone protects against uterine cancer

Most frequently prescribed drugs in the United States in 1990's

Marketed for prevention of heart disease and osteoporosis

1995: 58 million prescriptions
1999: 90 million prescriptions

Women's Health Initiative

- Started in 1991 and is ongoing today
- Phase I Randomized Controlled Clinical Trial comparing Premarin or Prempro vs. placebo

  >16,000 in Prempro arm

  >10,000 in Premarin arm

  - Primary Endpoint: Incidence of cardiovascular disease

Women's Health Initiative Findings

Does hormone therapy prevent coronary heart disease? NO

Risk of heart disease appeared to increase with HT

- Increased incidence in women over 60 and in first year of use (average age in study = 63)

Similar Results as the HERS study

Women's Health Initiative Findings

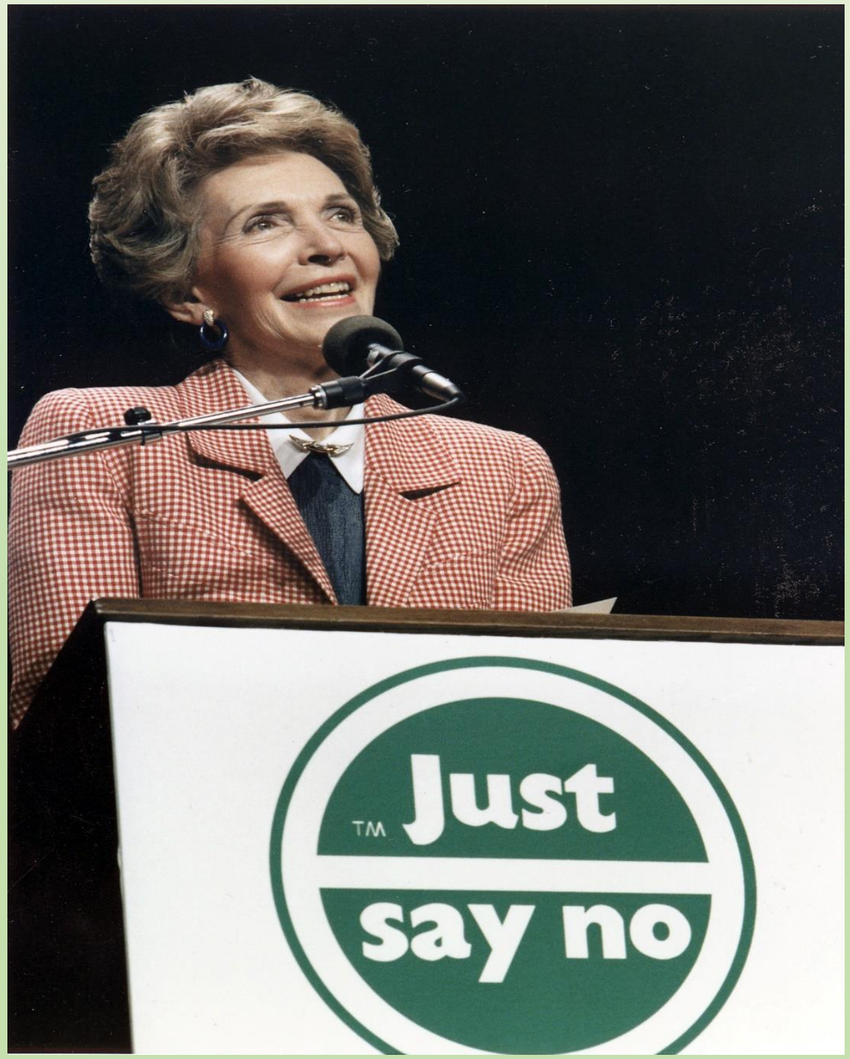
Secondary Endpoint: Risk of Breast CA

Safety threshold breached 2002

- Women taking Prempro had a slight increase in breast cancer
  - ➢ 8 more cases per 10,000 women <0.1% (rare event)
- Women taking Premarin had a statistically significant 23% *decrease* in breast cancer

WHI Study Results Released in 2002

The message received:



Black Box Warnings

FDA mandated in 2003

Included ALL estrogen-containing therapy for menopause

Led to a 70% decrease in usage of hormone therapy

FDA Black Box Warning

WARNING: CARDIOVASCULAR AND OTHER RISKS

Estrogens with and without progestins should not be used to prevent cardiovascular disease or dementia.

The Women's Health Initiative (WHI) study reported an increased risk of myocardial infarction, stroke, invasive breast cancer, and venous thromboembolism.

The Women's Health Initiative Memory Study (WHIMS) reported an increased risk of probable dementia in postmenopausal women 65 years of age or older.

MHT should be prescribed at the lowest effective dose for the shortest possible duration consistent with treatment goals and risks for the individual woman.

Guidelines for Hormone Therapy Use After WHI

Lowest dose

Shortest duration

Not to exceed 5 years

Were We Doing More Harm Than Good?

> **"The concept of "lowest dose for the shortest period of time" may be inadequate or even harmful for some women. A more fitting concept is "appropriate dose, duration, regimen, and route of administration."**

2017 Position Statement

The Menopause Society™

Reanalysis of WHI Data

No effect on breast cancer risk in women who had never used HT

It was the unusually low incidence of breast cancer in the placebo group of the WHI that created the "increased risk"

25% of women in placebo group had previously taken HT and had a *lower* breast cancer incidence than in the general population

WOMEN'S HEALTH INITIATIVE

Hodis and Sarrel Review
Climacteric, 2018 Dec.

Reanalysis of WHI Data

20-year follow-up of Premarin only arm →

Decreased breast cancer incidence persists!

Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials
JAMA July 28, 2020 Volume 324, Number 4

The Type of Estrogen Matters

Estradiol (E2) – "Bioidentical"

- ✓Binds to both *alpha and beta receptors*
- ✓Antiplatelet/positive lipid effects
- ✓Anti-inflammatory/antioxidant effects

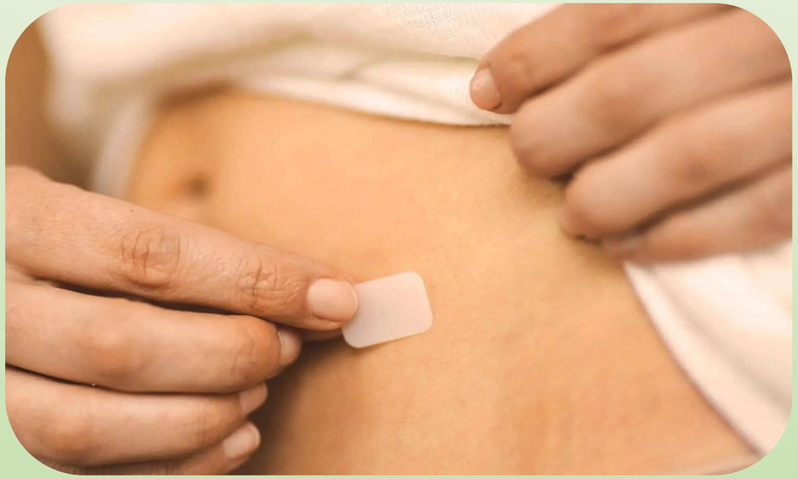
Premarin (Conjugated Equine Estrogen)

- Binds predominately to beta receptors
- Increases C-reactive protein
- Increases other pro-inflammatory markers

The Route of Estrogen Matters

- Transdermal estrogen (patch, gel, cream, or spray) is safer than oral estrogen

- NO increased risk of blood clot and stroke
  - With prior history of thrombosis
  - With genetic predisposition
  - With increased BMI



Sobel TH, Shen W. Transdermal estrogen therapy in menopausal women at increased risk for thrombotic events: a scoping review. Menopause. 2022 Jan

The Timing of Estrogen Matters

ELITE Study: Early vs. Late Treatment with Estradiol

- **No increased cardiovascular risks in either group but less coronary atherosclerosis in the early group (less than 6 years from menopause)**

WHI STUDY

- **40% lower heart attack risk and mortality rate in women initiating therapy between 50-59 years of age**

Critical Window Theory

"Timing Hypothesis":

Menopausal Hormone Therapy (MHT) provides cognitive and cardiovascular benefits only when initiated early

Later initiation of MHT may be ineffective or even harmful

Brain Health

Women's Health Initiative Memory Studies

Women aged 65-79 (WHIMS)

- **Prempro (CEE + MPA) doubled the risk of probable dementia**
- **Premarin (CEE) showed a "trend" toward increased risk**

Women aged 50-54 (WHIMS-Y)

- **No increased risk, but**
- **No positive effects on global cognition either**

Re-thinking Hormone Therapy

"Observational data and reanalysis of older studies by age or time since menopause, including the WHI, suggest that for healthy women who are within 10 years of menopause transition and have bothersome menopause symptoms, the benefits of hormone therapy (ET or EPT) outweigh its risks..."

2022 Position Statement

The Menopause Society™

FDA Black Box Warnings Removed

November 2025:

Removed from ALL estrogen containing menopausal therapy

Public perception is that MHT is now “safe”

Indications for Menopausal Hormone Therapy

Treatment of vasomotor symptoms (hot flashes, night sweats)

Prevention of osteoporosis

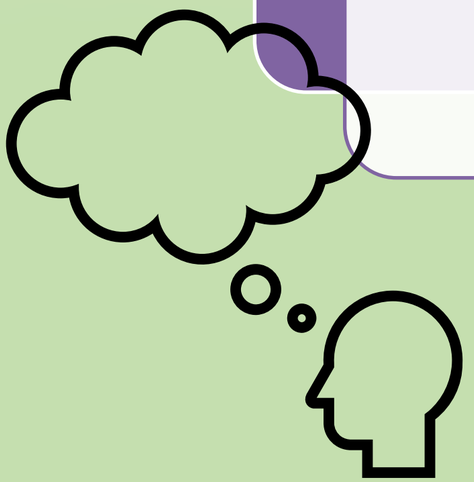
Benefits of Menopausal Hormone Therapy

Less Type II Diabetes

Not a preventative for cardiovascular disease

Benefits of Menopausal Hormone Therapy

Improvements in mood and cognition



Not a preventative for dementia

Why Hormone Therapy Matters

Leading Causes of Death in All Women

#1 Cardiovascular Disease 21.8%

#2 Cancer 20.7%

Lung	1:17	23% 5 yr survival
Breast	1:8	89% 5 yr survival
Colorectal	1:25	65% 5 yr survival

#3 Stroke 6.2%

Underlying Cause of Death in Women Over 65+

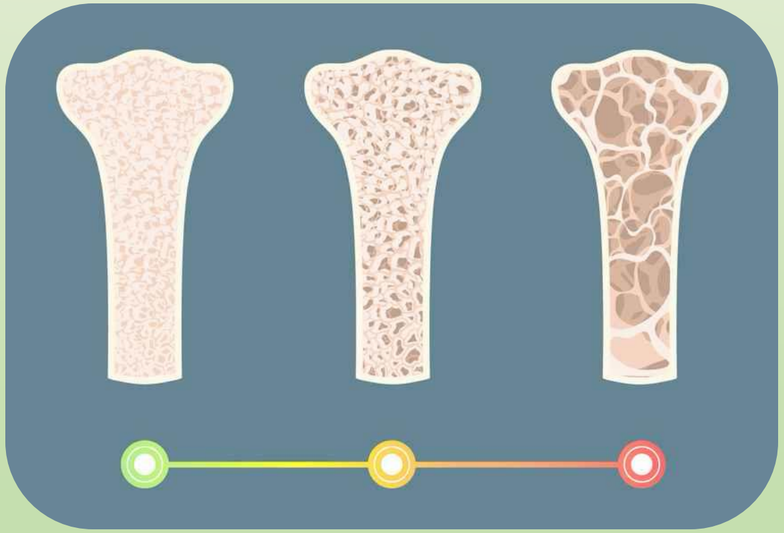
Osteoporosis

20% of women die within one year of hip fracture

Why Osteoporosis Matters

Per US Surgeon General:

- 8 million women have osteoporosis
- Twice the number that have breast cancer
- Estimated that 1 in 2 women will have a fragility fracture (vertebral, distal arm, hip)



- Prevalence in American women increased from 14% in 2008 to 20% in 2025
- No increase in men during the same time period

Components of Hormone Therapy

E1 Estrone sulfate

Aromatization of DHEAS in adipose tissue

Primary estrogen of menopause

Weaker than estradiol

E2 Estradiol

Produced by granulosa cells in ovary

Most biologically available and potent estrogen

Menopausal levels can be non-detectable

E3 Estriol

Produced in the placenta (very small amounts in the adrenal gland)

Weakest of estrogens

E4 Estetrol

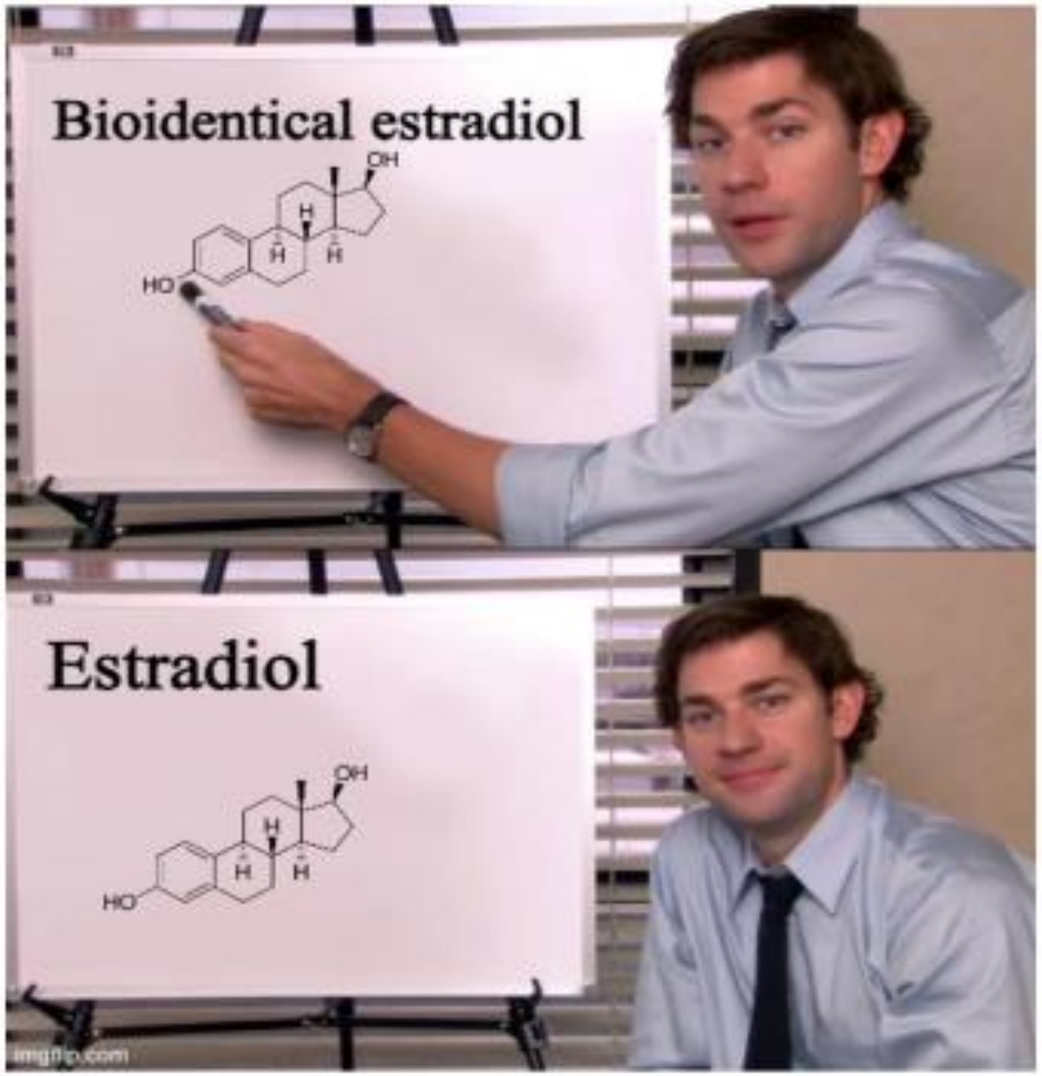
Produced in the fetal liver—both agonist and antagonist activity

Natural Estrogen with Selective action in Tissue (NEST)

Estradiol is Estradiol

Bioidentical Hormones

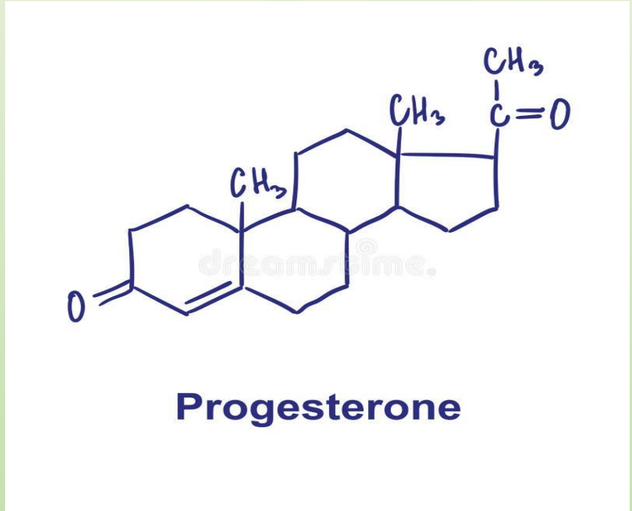
Courtesy of Dr. Jen Gunter
The Vagenda



Components of Hormone Therapy

Progesterone

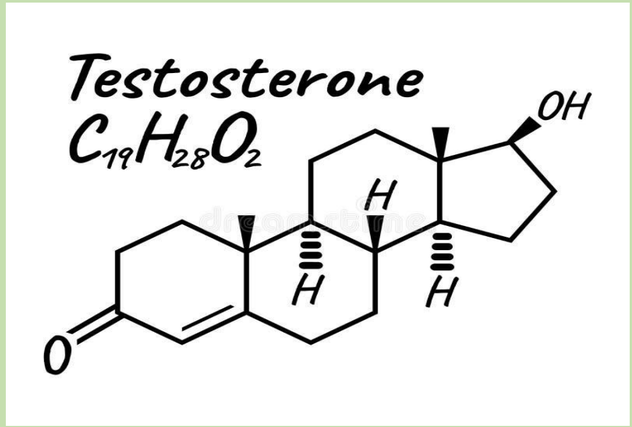
- Only produced in the ovary after ovulation
- Protects endometrium from hyperplasia, cancer
- Natural progesterone has sedative properties-- can help sleep
- Progestins are synthetic and more potent



Progesterone

Testosterone

- Small amounts still produced in postmenopausal ovary
- Free levels increase in menopause due to drop in SHBG
- May increase libido
- Androgen receptors in lower genital tract & bladder



Components of Hormone Therapy

SERMS

Selective Estrogen Receptor Modulators

Anti-estrogenic on breast

Estrogenic on bone

Uses in Menopause RX

Raloxifene– decrease in lumbar fractures but not hip

Ospemifene—for genitourinary syndrome of menopause

Bazedoxifene—endometrial protection (only in Duavee)

Systemic Estrogen Preparations

Conjugated Estrogen derivatives
- Equine—Premarin
- Non-equine—
  - Menest
  - Ogen
  - Cenestin

Estradiol
- Pills—Estrace
- Rings—Femring
- Patches—Climara, Alora, Vivelle, Minivelle
- Gels—Estrogel, Elestrin, Divigel
- Spray—Evamist
- Lotion--Estrasorb

Progestogens

Prometrium--micronized progesterone (has peanut oil)
Provera—medroxyprogesterone acetate
Norethindrone “Mini-pill”
Aygestin—norethindrone acetate (weak estrogen effect)
Slynd—drosperinone
Levonorgesterel IUD (52 mg only)—studied up to 5 years

Systemic Estrogen Progestogen Preparations

Oral

- Prempro—CEE + MPA
- Activella—estradiol + norethindrone acetate
- FemHRT—ethinyl estradiol + norethindrone
- Angeliq– ethinyl estradiol + drosperinone
- Bijuva –estradiol + progesterone capsules
- Duavee—conjugated estradiol + bazedoxifene

Transdermal

- Combipatch—estradiol + norethindrone actetate (bi-weekly)
- ClimaraPro—estradiol + levonorgestrel (weekly)

Systemic Estrogen/Testosterone

Estratest (esterified estrogens + methyltestosterone)

- Generic = Syntest
- Not FDA approved but available since 1965
- Available in 2 strengths
- Methyltestosterone does not metabolize to estrogen
- Methyltestosterone has been used to treat metastatic breast CA

Hormone Treatment Options for Older Women

To improve bone health without increasing cardiovascular or dementia risks

SERMS - Selective Estrogen Receptor Modulators

- Prevents bone loss
- Does not stimulate breast tissue
- Raloxifene (Evista) FDA approved
- Decreased vertebral fractures
- Increase DVT risk (1.2/1000)

Ultra low dose Estradiol

- 14 mcg patch
- Not systemic hormone therapy
- Does not need added progestogen
- Yearly progestin challenge recommended
- Menostar FDA approved

Non-hormonal options

For hot flashes in women who are not candidates for hormone therapy

SSRI's and SSNRI's :

- Brisdelle (7.5 mg paroxetine)
- Venlafaxine (37.5 or 75 mg)

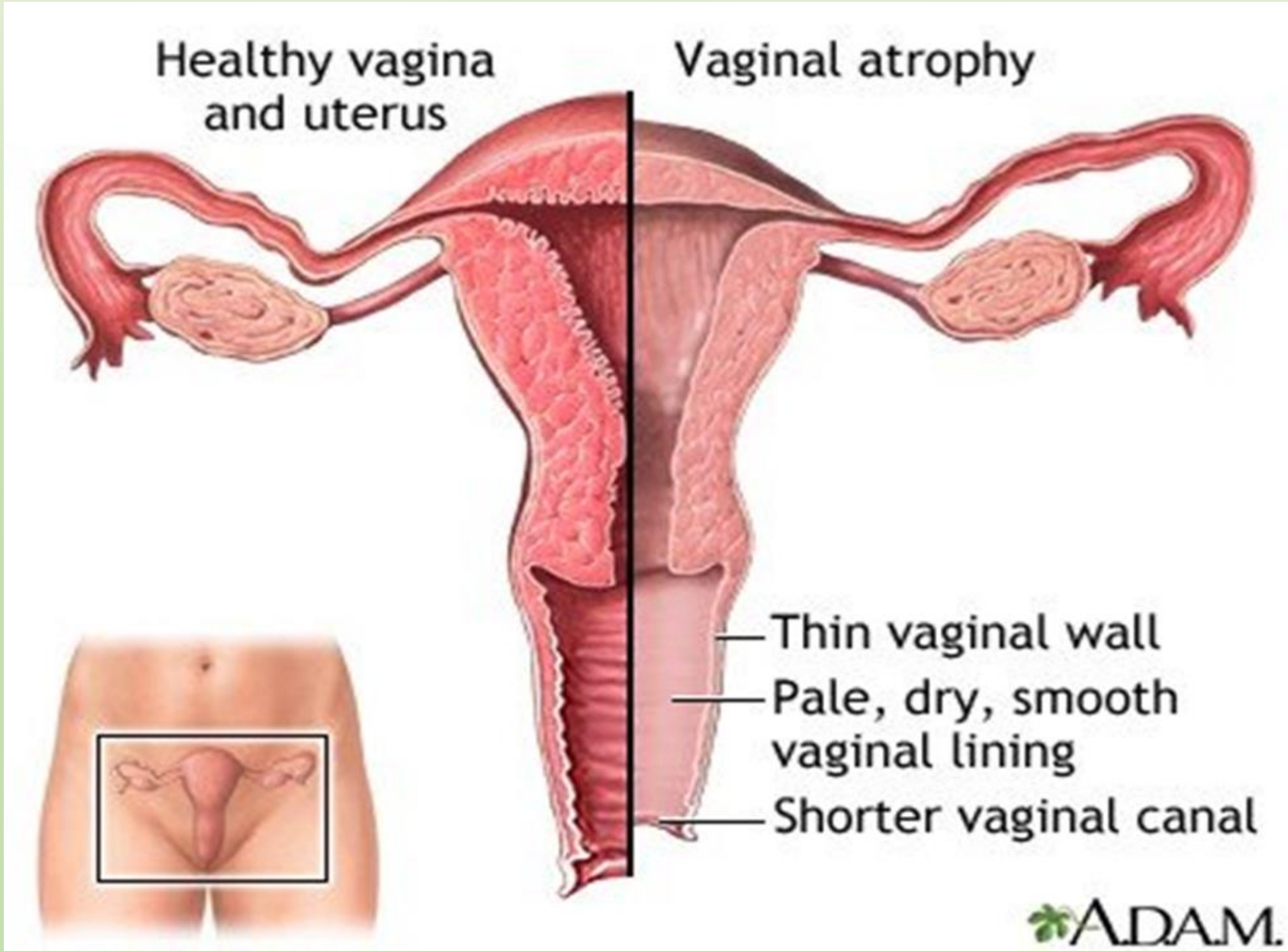
Clonidine patches →may lower BP

Gabapentin, oxybutynin → may offer relief for some

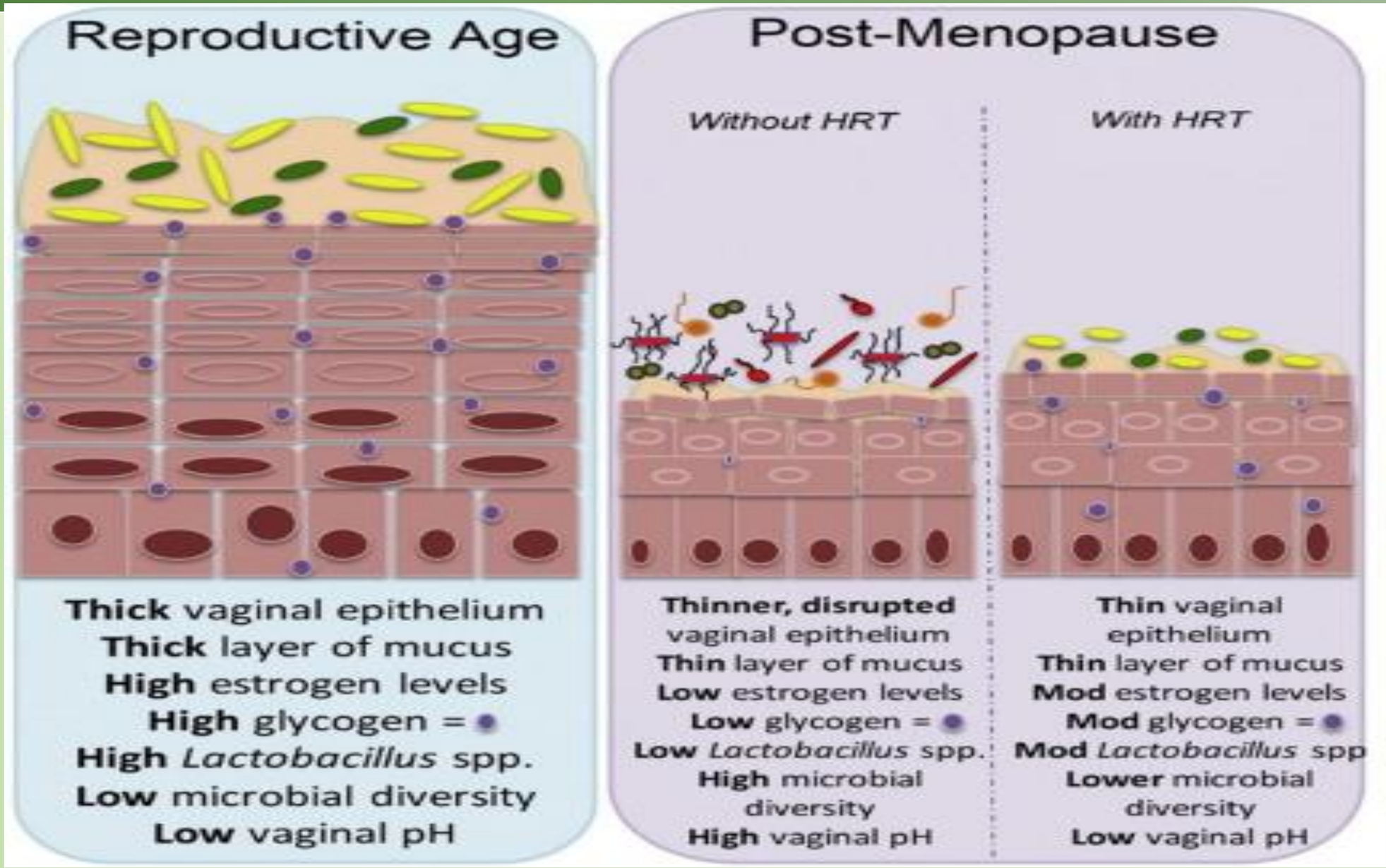
Neurokinin antagonists:

- Fezolinetant (NK 3)—must monitor LFTs for one year
- Elinzanetant (NK 1,3)—monitor LFTs for 3 months

Genitourinary Syndrome of Menopause



Changes in Microbiome



Benefits of Vaginal Estrogen/Androgen

Less Urinary Tract Infections

- more good bacteria
- improves muscle function so better bladder emptying

Less Urinary Incontinence

- improvements in both stress (leakage) and
- urge incontinence (loss of bladder control)

Less “spraying”

Less dryness and pain

More blood flow to the genitalia

Better sex

Local Vaginal Hormone Therapy

Estrogen

- *Creams (Estrace, Premarin)—two-three times weekly*
- *vaginal tablets (Vagifem/Yuvafem)—two-three times weekly*
- *Vaginal suppositories (Imvexxy)—two-three times weekly*
- *vaginal ring (Estring)—replace every 3 months*

DHEA (metabolizes to estrogen + testosterone)

- *Suppositories (Intrarosa)—nightly*

SERMS (selective estrogen receptor modulators)

- *Ospemifene (Osphena) –daily oral tablet*

What About Perimenopause?

We treat the symptoms, not the lab work

Estrogen levels are “normal” – fluctuations can cause significant symptoms

Treatment options: low dose oral contraceptives or hormone therapy

Do NOT have to wait until 12 months without a period to start treatment!

What About Perimenopause?

Perimenopause symptoms vary widely, but not all symptoms respond to treatment

- Hot flashes
- Night sweats
- Vaginal dryness
- Brain fog

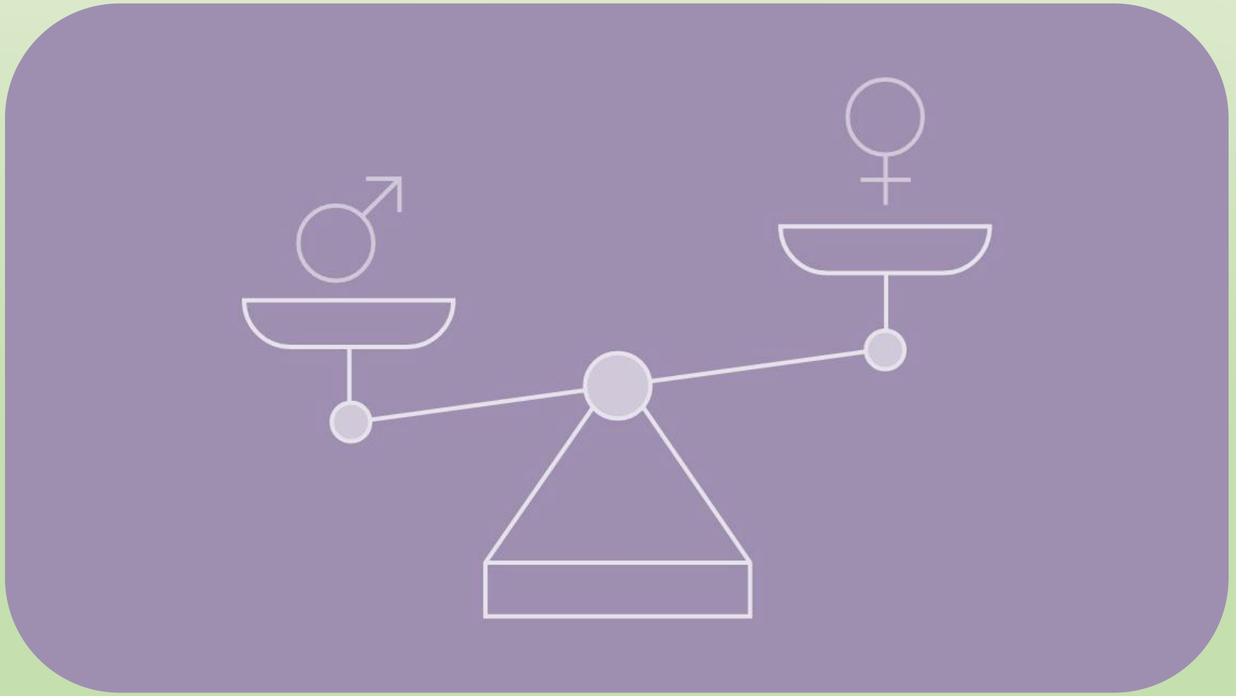
- Weight gain
- Joint pain
- Sleep
- Anxiety
- Palpitations

Misinformation About Hormones

Need to “check” your hormones

Need to “balance” your hormones

Need to treat “low” levels



Pitfalls of lab testing

Commercially available lab studies:

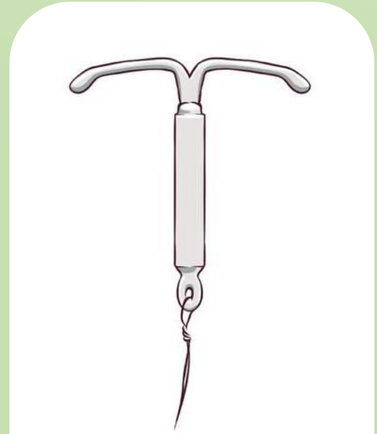
- Not accurate if taking oral birth control pills or oral forms of HT
- Interference from other drugs/supplements (biotin, etc)
- Perform poorly at the lower end of the hormone range

- Progesterone levels not clinically useful

When are Laboratory Studies Useful?

If unable to assess menstrual pattern

- History of endometrial ablation
- Use of hormonal IUD
- History of hysterectomy



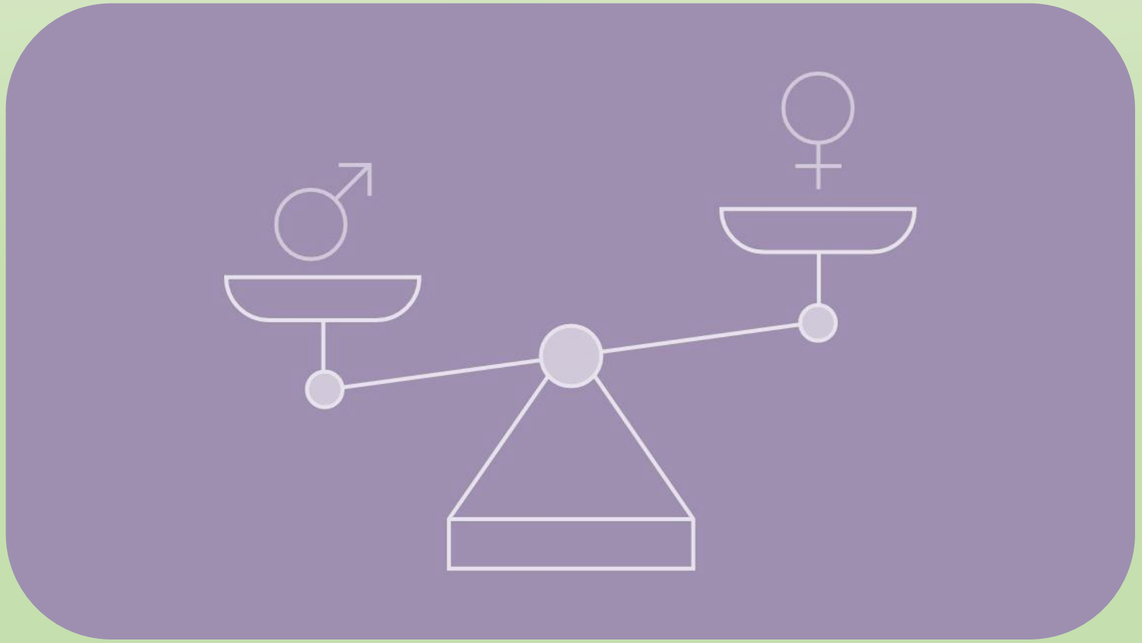
Hormonal IUD

Do You Need to "Balance" Your Hormones?

Hormone "balancing" often means people are given a cocktail of hormones including progestogens

What to know about progestogens:

- Includes natural progesterone, synthetic progestins and IUDs
- Must be included for women who have a uterus
- Dose is set by studies NOT lab work levels
- Slight increase in breast cancer incidence



Testosterone

What About “Low” Testosterone?

Testosterone in Women

- Decreases slowly from age 18-60
- Increases slightly after age 60
- Testosterone treatment:
  - Indicated only for low libido (after other causes ruled out); NOT indicated for increased energy
  - Not FDA-approved for women; no long-term safety data
  - No improvement in muscle or bone mass
  - Side effects: loss of scalp hair, growth of face and body hair, oily skin, acne, virilization

Menopause Society Position Statement

Cardiovascular Health

2022 Observational data and reanalysis of older studies by age or time since menopause, including the WHI, suggest that for healthy women who are within 10 years of menopause transition and have bothersome menopause symptom, the benefits of hormone therapy (ET or EPT) outweigh its risks with fewer CVD events in younger v. older women

Menopause Society Position Statement

Breast Health

2017: A rare absolute risk of breast cancer (< 1 additional case/1,000 person-years of use) was seen with CEE +MPA in the WHI-- a risk slightly greater than that observed with one daily glass of wine, less than with two daily glasses, and similar to the risk reported with obesity, low physical activity, and other medications.

A statistically significant reduction of breast cancer risk resulting from CEE in the WHI was observed overall in women who were at least 80% compliant with therapy

2022: Compared with placebo or non-users, there appears to be no additive effect with age or elevated personal breast cancer risk factors

Menopause Society Position Statement

Bone Health

- Hormone therapy has been shown in RCTs to prevent bone loss and in the WHI was shown to reduce fractures in postmenopausal women without osteoporosis
- HT is indicated for prevention but not for treatment with dose related effects on bone density (according to ISCD 50 pg/ml is ideal level)
- Unless contraindicated, women with POI or premature menopause without osteoporosis or a fragility fracture are best served using HT for prevention and reduction in fracture risk rather than bone specific treatments until the average age of menopause

Summary

For Women within 10 years of menopause or under age 60

- May treat symptomatic women prior to the last menstrual period
- Systemic Menopausal HT has more benefits than risks
- Transdermal estradiol has fewer risks than oral estrogens
- Compatible with cardiovascular and brain health but not a preventative treatment
- No set time limit for use but medical contraindications exist

My List of Do's and Dont's

Do: Treat **ALL** women under age 45 with HT unless absolutely contraindicated
Treat or refer all **symptomatic** women unless absolutely contraindicated
Prescribe vaginal estrogen to any women who will use it

Don't: Order hormone levels & treat because they are "too low"
Treat low energy and muscle mass with testosterone
Stop hormone therapy at age 65
Rule out HT for patients with family history of breast cancer
migraine headaches with aura
history of VTE

Refer **asymptomatic** women who are > 10 years beyond menopause for HT use because they want the benefits of HT –data do not support

Summary

For Women older than age 60 and > 10 years after menopause

Systemic hormone therapy may increase risks

- **Cardiovascular disease**
- **Dementia**

Safe treatment options may include

- **Local vaginal estrogen therapy**
- **SERMS**
- **Ultra-low dose transdermal estradiol**

Questions?

Thank you!

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