Progesterone: The Goldilocks Hormone for Perimenopausal and Menopausal Women

Presented by Dr. LaKeischa McMillan

Objectives

1. **Introduction.**

2. Review Progesterone's Role in the Menstrual Cycle.

3. Explore All the Organ Systems that make Progesterone.

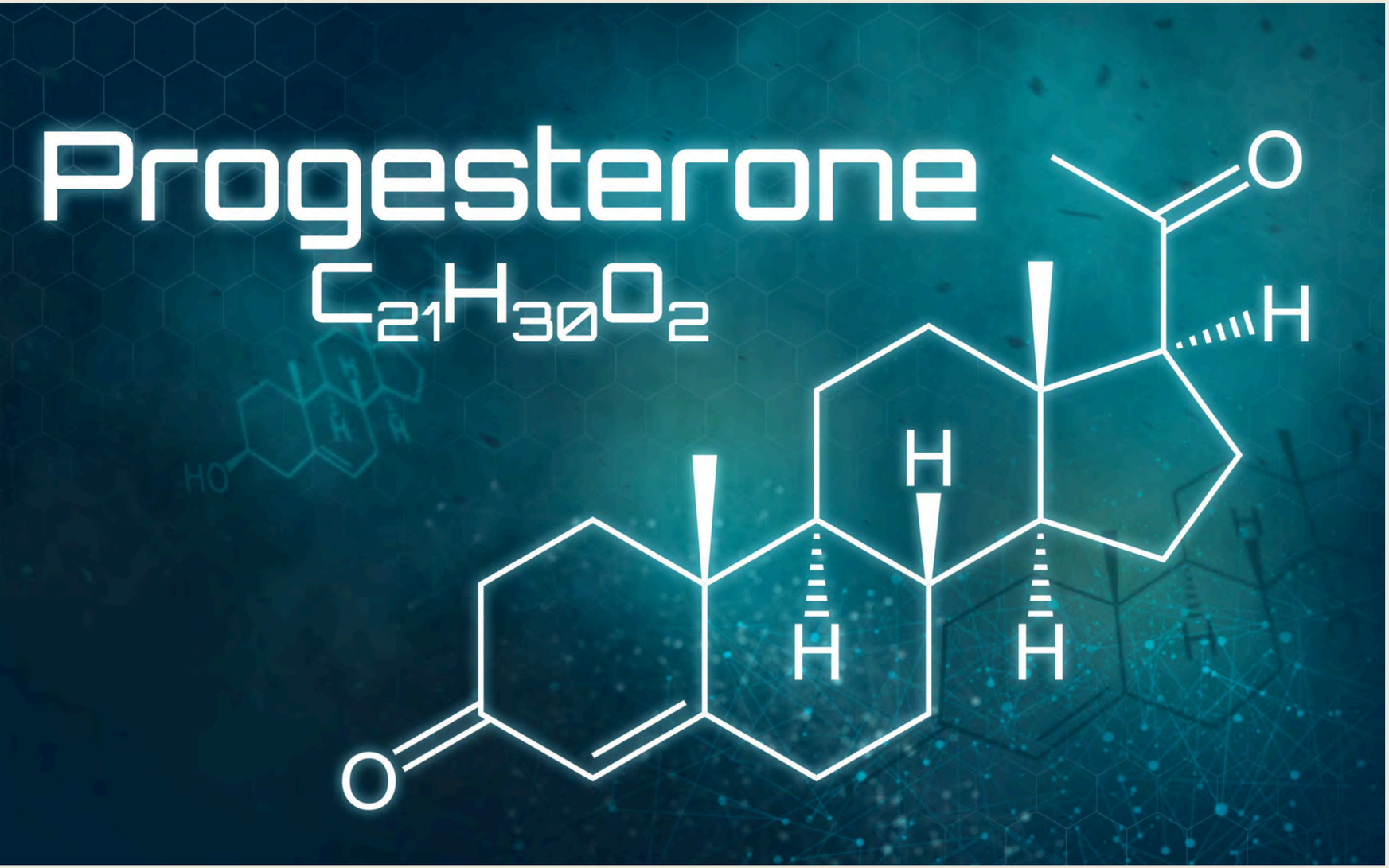
4. Progesterone as a Sleep Aid.

5. Progesterone Nature's Xanax.

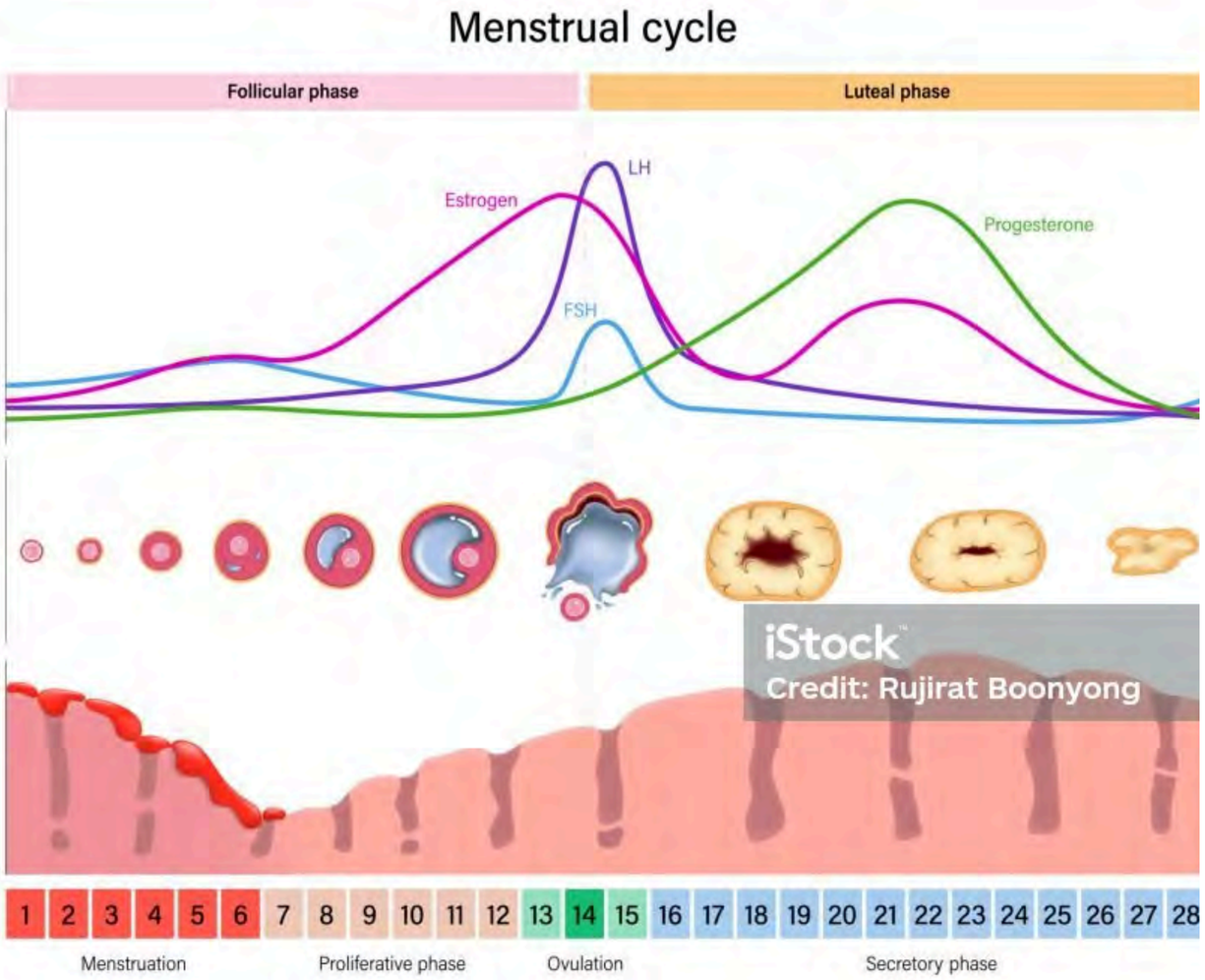
6. Progesterone and Weight Gain.

The Key Takeaways for the Lecture

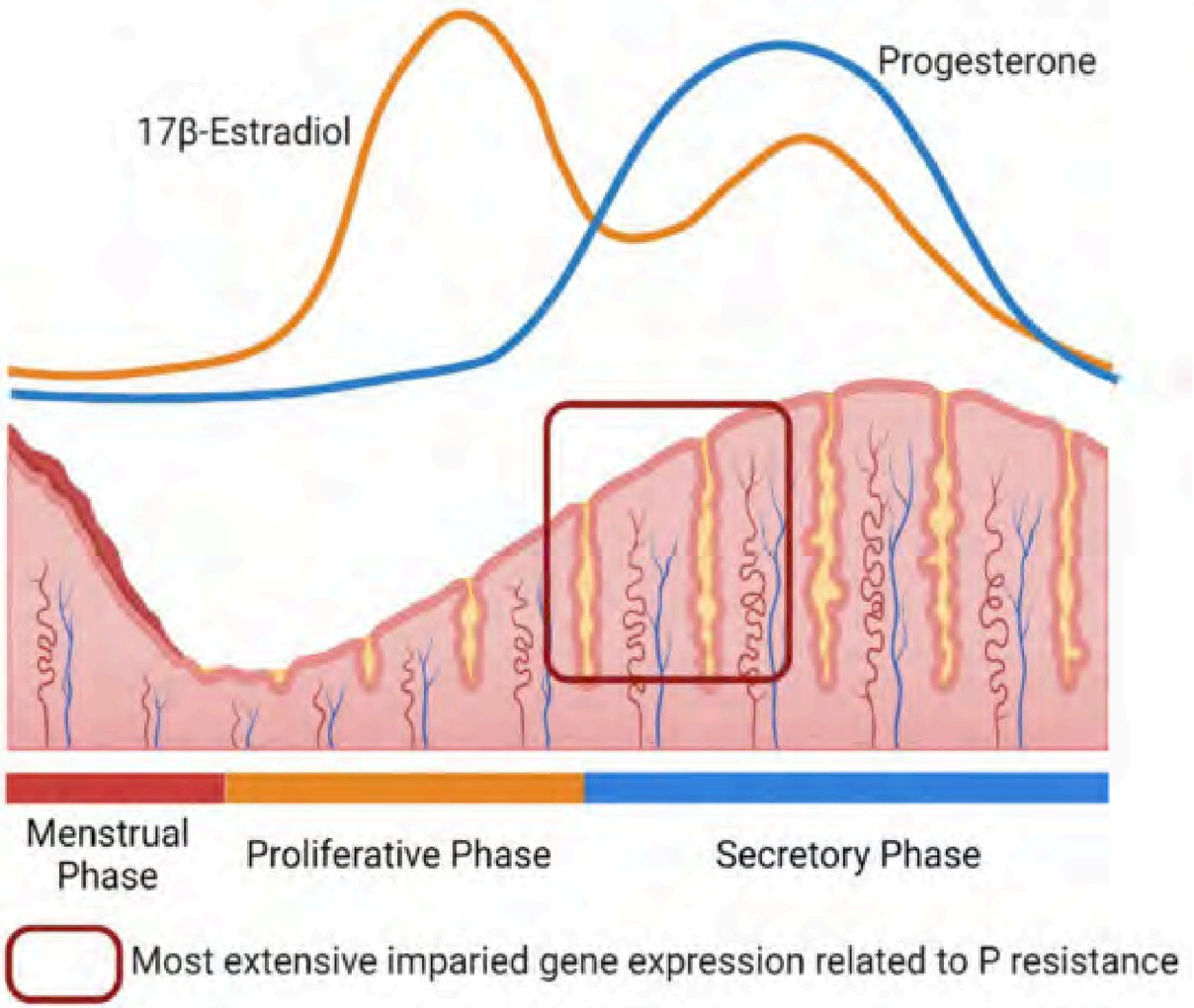
- **A paradigm shift: Think of estrogen dominance as progesterone deficiency.**
- **Be aware that progesterone influences the brain as well as the uterus.**
- **Begin to think of progesterone as nature's Xanax.**
- **As you would with estrogen be aware of how the body synthesizes and metabolizes progesterone.**
- **Bring progesterone into the conversation sooner than later with perimenopausal women.**



Hormones and The Cycle



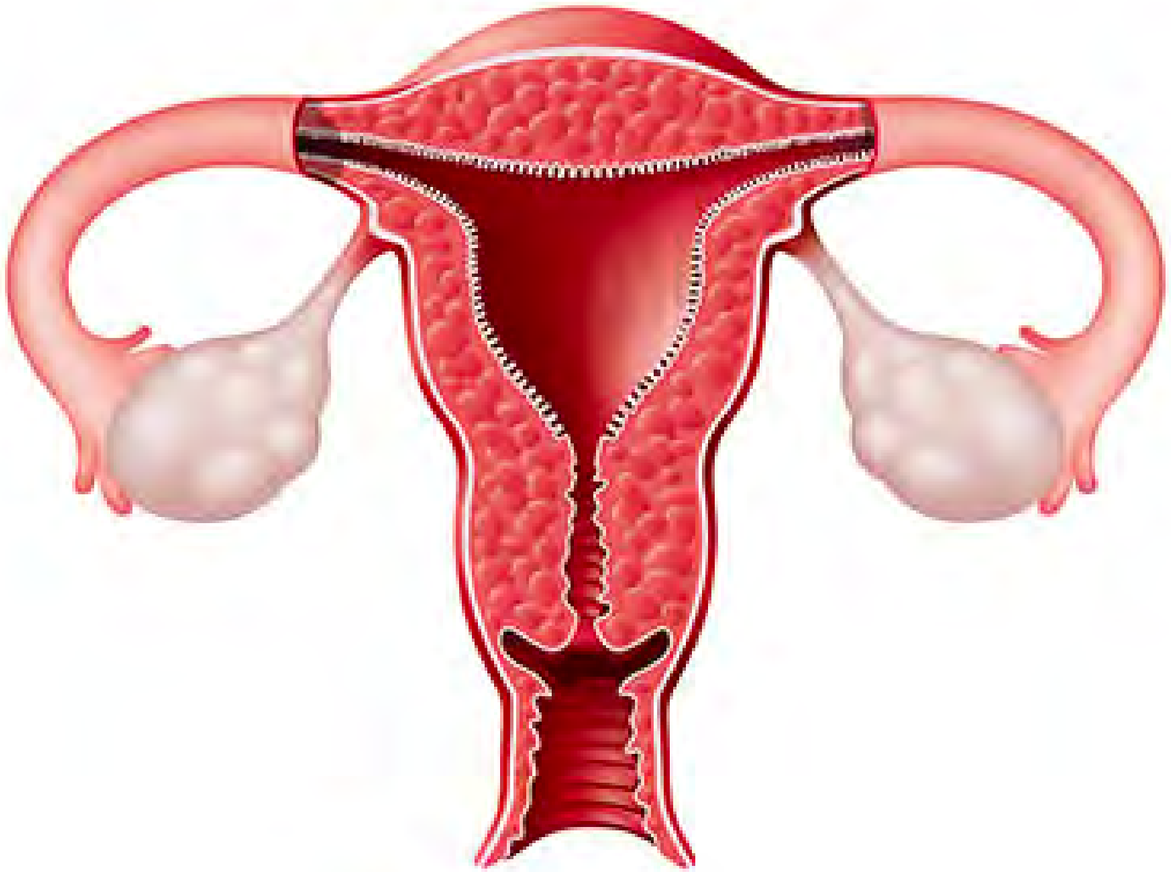
Progesterone’s Effect on the Endometrium



"Think of your period this way. Estrogen is in charge of making the grass grow tall. This is the uterine lining getting thick and ready for a fertilized egg to come and grow. Progesterone is in charge of mowing the grass. Depending on how high the grass is will determine how heavy the flow is. "

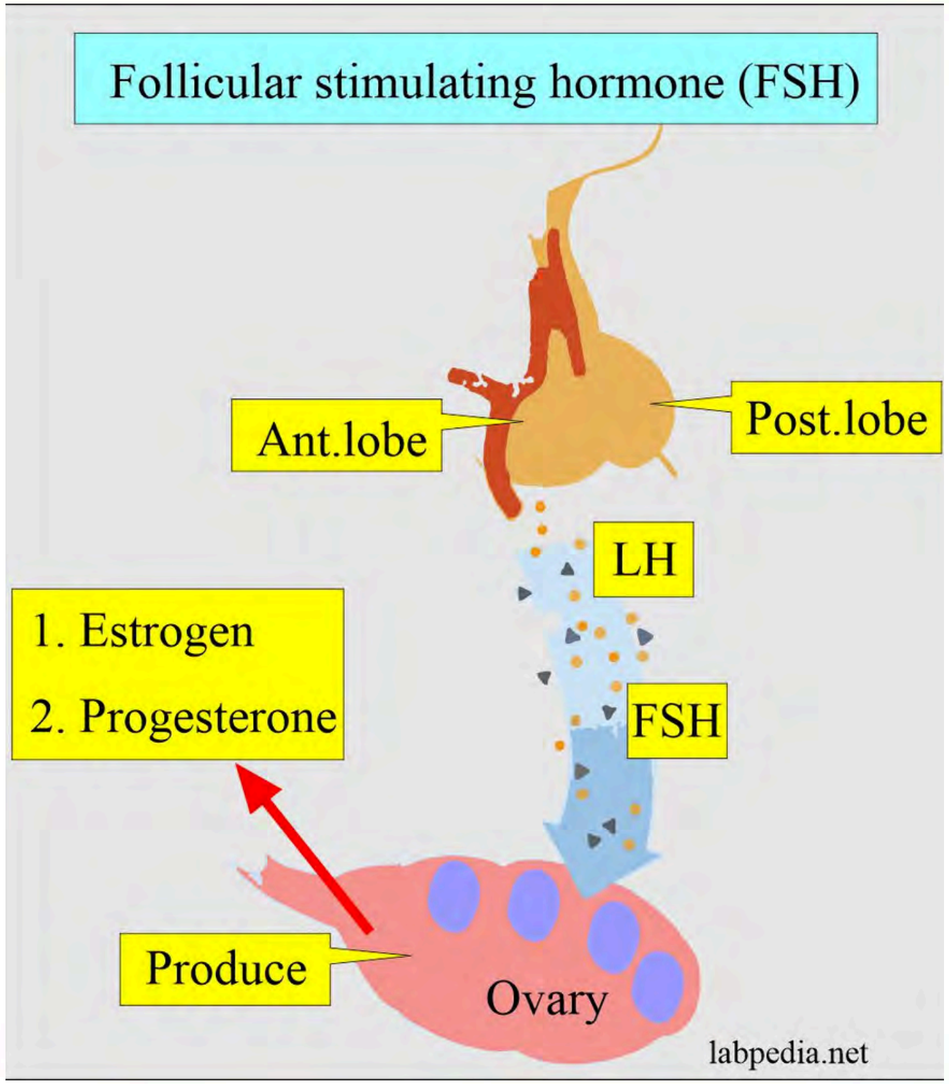
~ Dr Lakeesha ~

No Uterus No Progesterone



Progesterone Synthesis

- **Progesterone is synthesized in the ovary at the site of the corpus luteum**
- **Progesterone is produced by the placenta during pregnancy with surges happening around the 14th week of gestation.**
- **Another site of progesterone production is the adrenal glands**
- **Progesterone is also synthesized in the nervous system by neurons and glial cells.**



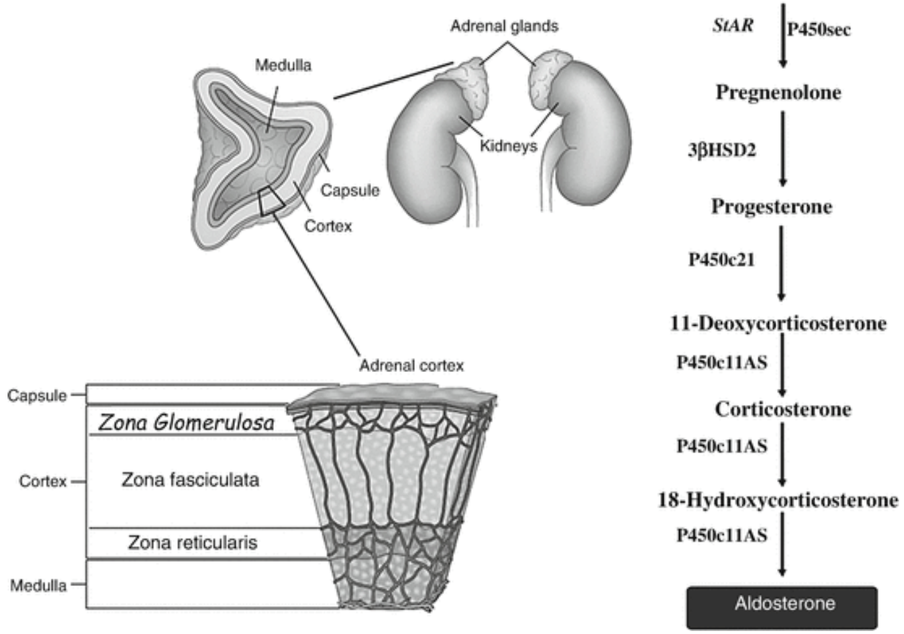
Progesterone Synthesis in the Adrenal Glands

In the Adrenal Cortex in two areas:

The Zona Fasiculata
The Zona Glomerulosa

The Synthesis of 4 Neuroactive Steroids Occurs.

1. Allopregnanolone
2. Isopregnanolone
3. Pregnanolone
4. Epiprenanolone



These neuroactive steroids can cross the blood-brain barrier.

Progesterone and the Brain.

PRs are located in the following areas of the brain:

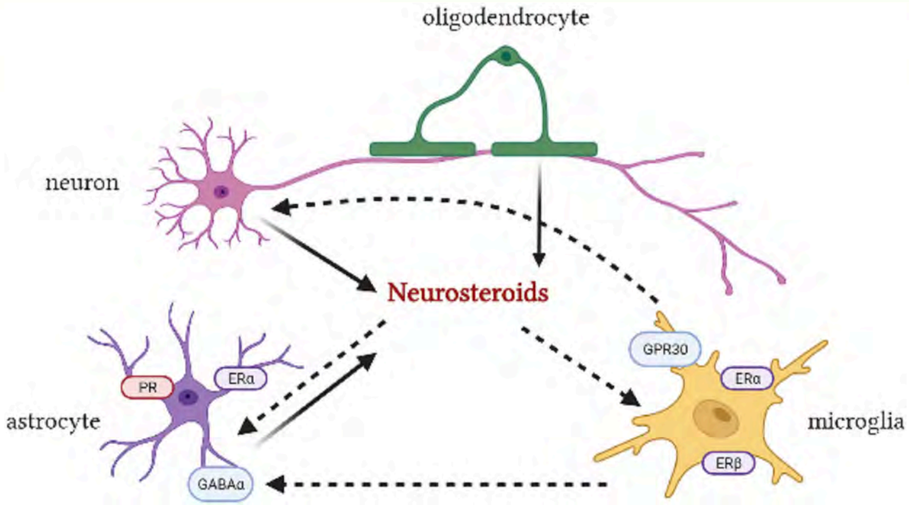
1. Hypothalamus

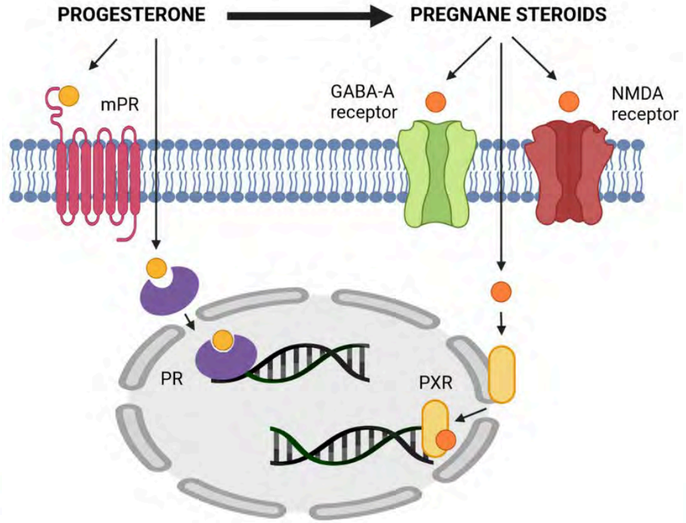
2. Amygdala

3. Hippocampus

4. Thalamus

5. Frontal Cortex





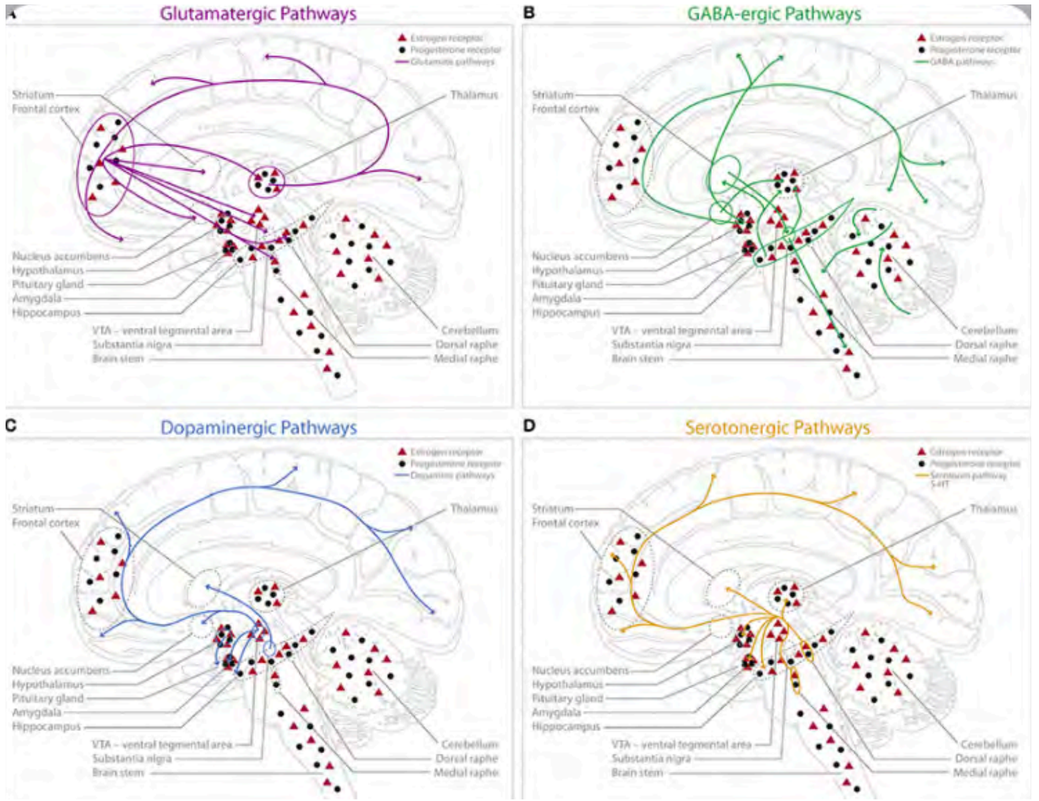
Progesterone and the Brain (con’t)

Progesterone and Neuroactive steroids have been shown to further modulate neurotransmitter systems such as:

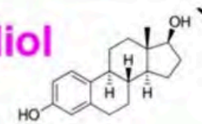
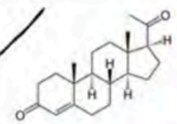
1. Serotonergic

2. Cholinergic

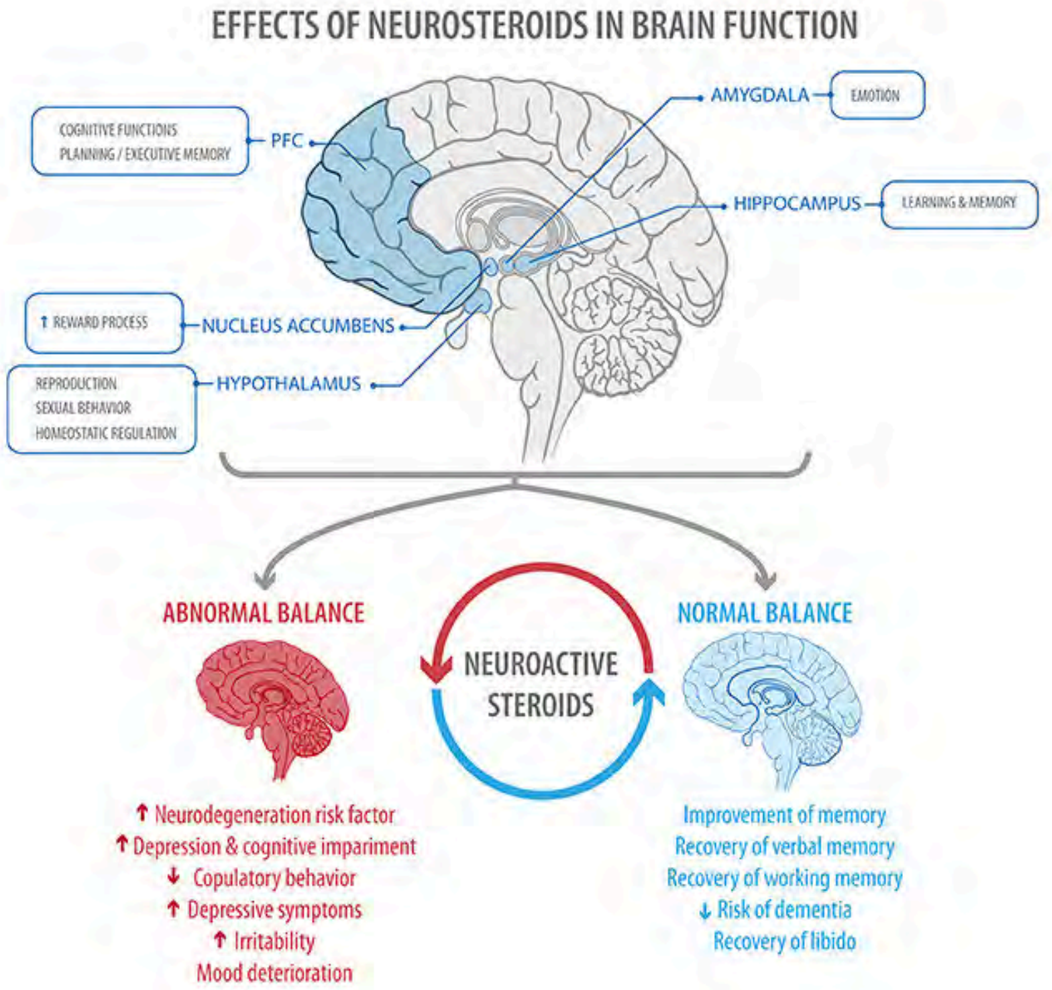
3. Dopaminergic



What are the Benefits of Progesterone?

	Estradiol E2 	 Progesterone P4
Cells and Tissues	**Growth with Proliferation**	**Maturation with ↓ Proliferation**
Uterus–Endometrium	Proliferative	Secretory
Uterus–Cervix	↑ Mucus Volume and Stretch	↓ Mucus Volume and Stretch
Breast–Epithelial	Proliferation	↓ Proliferation, Maturation
Breast–Lobular Alveolar (Areola and Nipple)	↑ Breast Volume	↑ Areolar Size
Bone Remodeling	↓ Resorption	↑ Formation
Cardiovascular—Vascular Endothelial Function	↑ FMD	↑↑ FMD
Cardiovascular—Electrical Function, QT	↑ QT Interval	↓ QT Interval
Brain	Excitation/Activation	Excitation/Calming
Sleep	?	↑ Deep Sleep
Central NE	↑	Likely ↓

What are the Benefits of Progesterone? (con't)



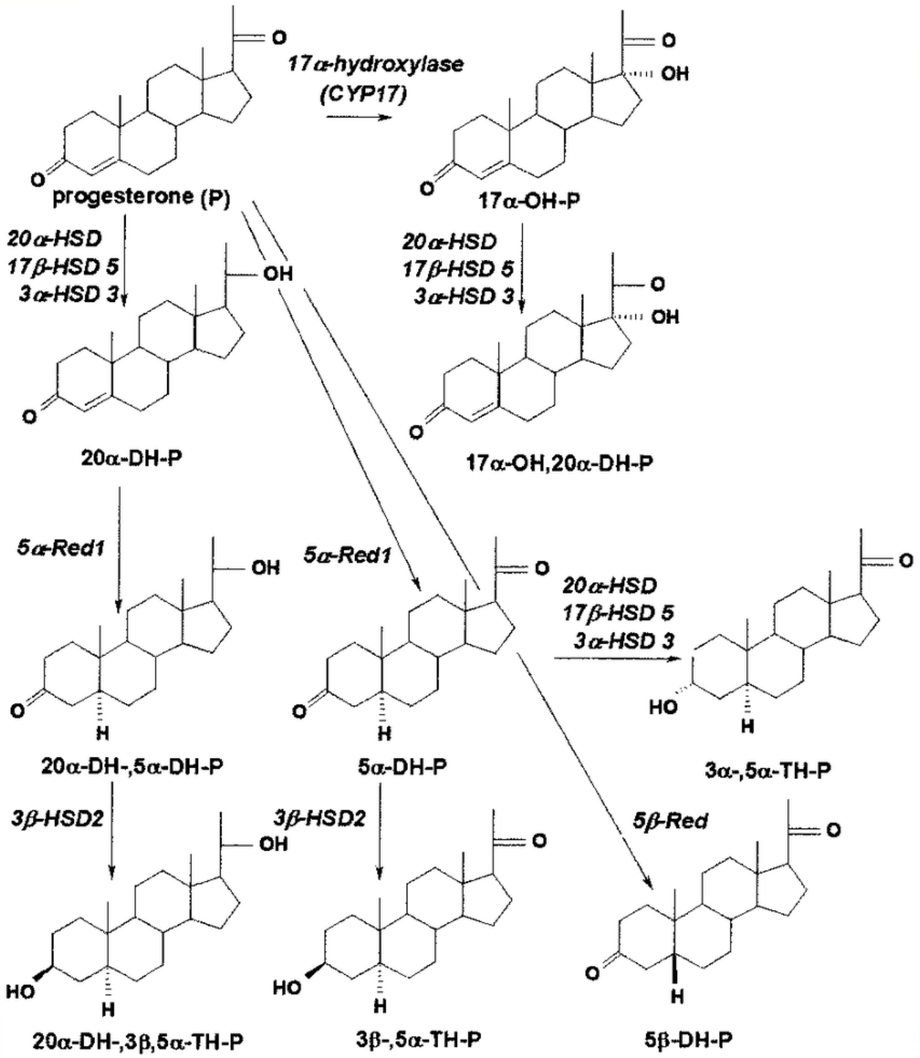
Signs and Symptoms of Progesterone Deficiency

- Hot flashes
- Night sweats
- Vaginal dryness
- Foggy thinking
- Memory lapses
- Incontinence
- Depressed
- Anxiety
- Sleep disturbances
- Heart palpitations
- Water retention
- Premenstrual syndrome
- Early miscarriages
- Cyclical headaches
- Painful or lumpy breasts
- Infertility

What Happens When Progesterone is Too High?

Progesterone:
The Goldilocks Hormone for Perimenopause and Menopause

Progesterone Metabolism



The Key Takeaways for the Lecture

- **A paradigm shift: Think of estrogen dominance as progesterone deficiency.**
- **Be aware that progesterone influences the brain as well as the uterus.**
- **Begin to think of progesterone as nature's Xanax.**
- **As you would with estrogen be aware of how the body synthesizes and metabolizes progesterone.**
- **Bring progesterone into the conversation sooner than later with perimenopausal women.**

Progesterone: The Goldilocks Hormone for Perimenopause and Menopause

Not All Progesterone Is Created Equal

Objectives

1. **What is Causing All the Confusion?**

2. **Progestins**

3. **Bio-identical Progesteone**

4. **Progesterone: How Should I Prescribe It?**

5. **What Test Should I Run to Follow Up?**

6. **How do I Adjust a Patient's Dosing?**

The Key Takeaways for the Lecture

- **A paradigm shift: Progesterone even when my patient has had a hysterectomy**
- **Help patients understand that there are different types of progesterone**
- **Consider continuous progesterone dosing.**
- **Remember the various ways to test progesterone levels.**

1.What is Causing All the Confusion?

It’s Not the WHI Study’s Fault

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

Principal Results From the Women’s Health Initiative Randomized Controlled Trial

Writing Group for the Women’s Health Initiative Investigators

Context Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

Objective To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States.

Design Estrogen plus progestin component of the Women's Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16 608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998.

Interventions Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n=8506) or placebo (n=8102).

Main Outcomes Measures The primary outcome was coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome. A global index summarizing the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

Results On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. This report includes data on the major clinical outcomes through April 30, 2002. Estimated hazard ratios (HRs) (nominal 95% confidence intervals [CIs]) were as follows: CHD, 1.29 (1.02-1.63) with 286 cases; breast cancer, 1.26 (1.00-1.59) with 290 cases; stroke, 1.41 (1.07-1.85) with 212 cases; PE, 2.13 (1.39-3.25) with 101 cases; colorectal cancer, 0.63 (0.43-0.92) with 112 cases; endometrial cancer, 0.83 (0.47-1.47) with 47 cases; hip fracture, 0.66 (0.45-0.98) with 106 cases; and death due to other causes, 0.92 (0.74-1.14) with 331 cases. Corresponding HRs (nominal 95% CIs) for composite outcomes were 1.22 (1.09-1.36) for total cardiovascular disease (arterial and venous disease), 1.03 (0.90-1.17) for total cancer, 0.76 (0.69-0.85) for combined fractures, 0.98 (0.82-1.18) for total mortality, and 1.15 (1.03-1.28) for the global index. Absolute excess risks per 10000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10000 person-years.

Conclusions Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.

JAMA. 2002;288:321-333 www.jama.com

THE WOMEN’S HEALTH INITIATIVE (WHI) focuses on defining the risks and benefits of strategies that could potentially reduce the incidence of heart disease, breast and colorectal cancer, and fractures in postmenopausal women. Between 1993 and 1998, the WHI enrolled 161 809 postmenopausal women in the age range of 50 to 79 years into a set of clinical trials (trials of low-fat dietary pattern, calcium and vitamin D supplementation, and 2 trials of postmenopausal hormone use) and an observational study at 40 clinical centers in the United States.[1] This article reports principal results for the trial of combined estrogen and progestin in women with a uterus. The trial was stopped early based on health risks that exceeded health benefits over an average follow-up of 5.2 years. A parallel trial of estrogen alone in women who have had a hysterectomy is being continued, and the planned end of this trial is March 2005, by which time the average follow-up will be about 8.5 years.

The WHI clinical trials were designed in 1991-1992 using the accumulated evidence at that time. The primary outcome for the trial of estrogen plus progestin was designated as coronary heart disease (CHD). Potential cardioprotection was based on generally

For editorial comment see p 366.

Author Information and Financial Disclosures appear at the end of this article.

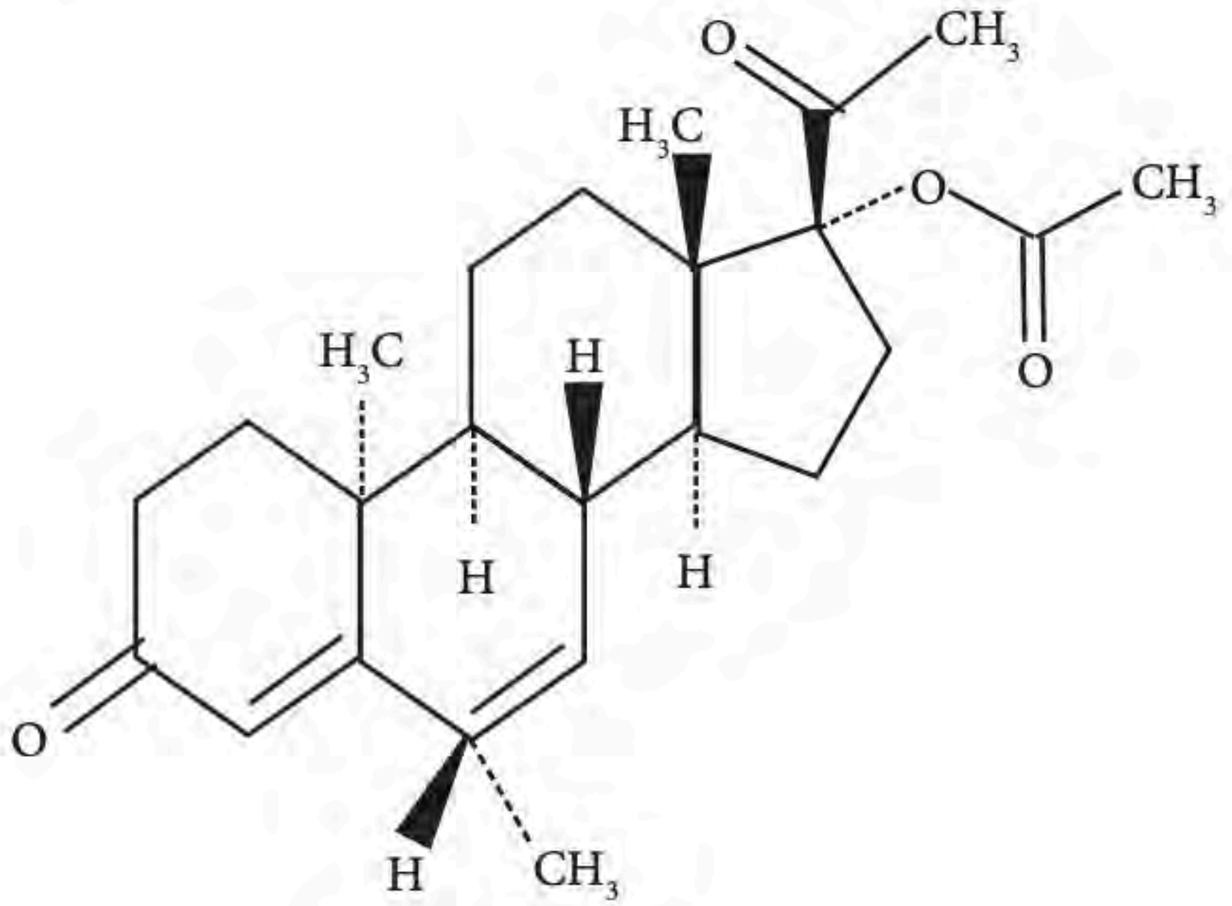
Misuse of Terminology

- **ProgestOGEN --** " any substance, natural or synthetic, that exerts progesterone-like activity via the activation of the progesterone receptor (PR)."

- **ProgesTIN**--"synthetic versions of progesterone”

2.Progestins

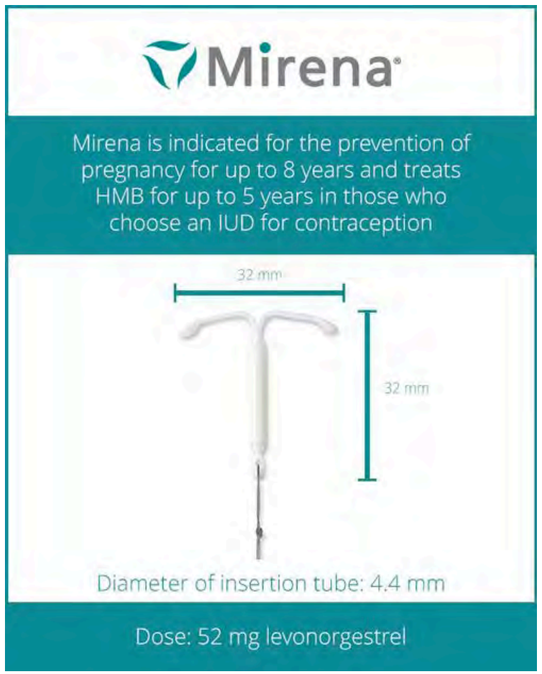
Figure 3. Structure of Medroxyprogesterone Acetate

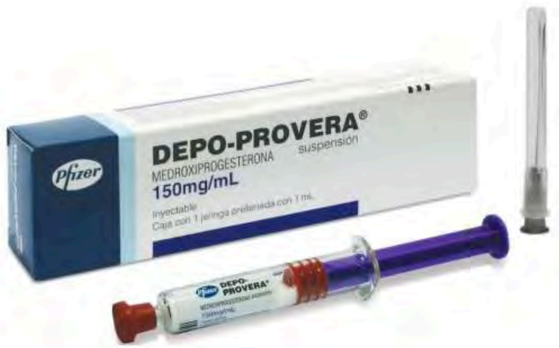


Let’s Get Some Clarity

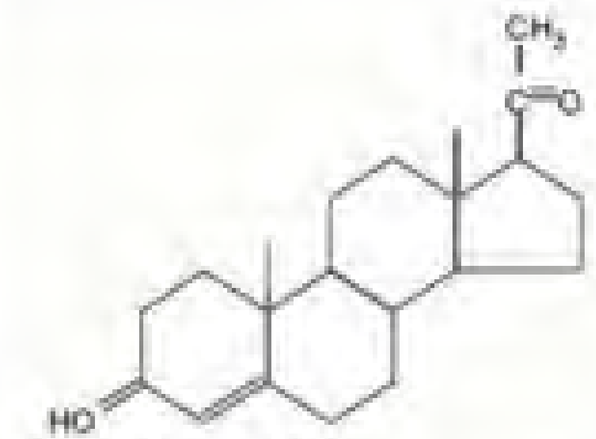
Clinically available forms of ProgesTINS

1. **Medroxyprogesterone acetate (MPA)**
2. **Levonorgestrel**
3. **Norethindrone acetate (NETA)**

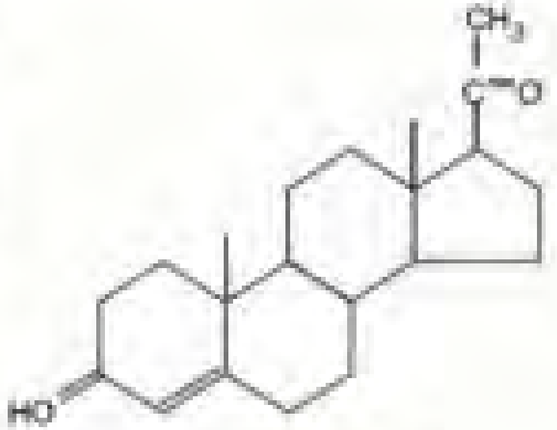




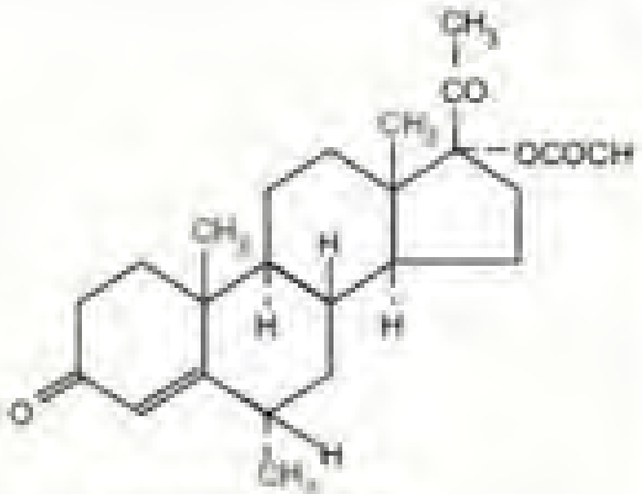
3.Bio-identical Progesterone



Bioidentical Progesterone



Human Progesterone



Provera(MPA)

Figure 1. Structure of Progesterone

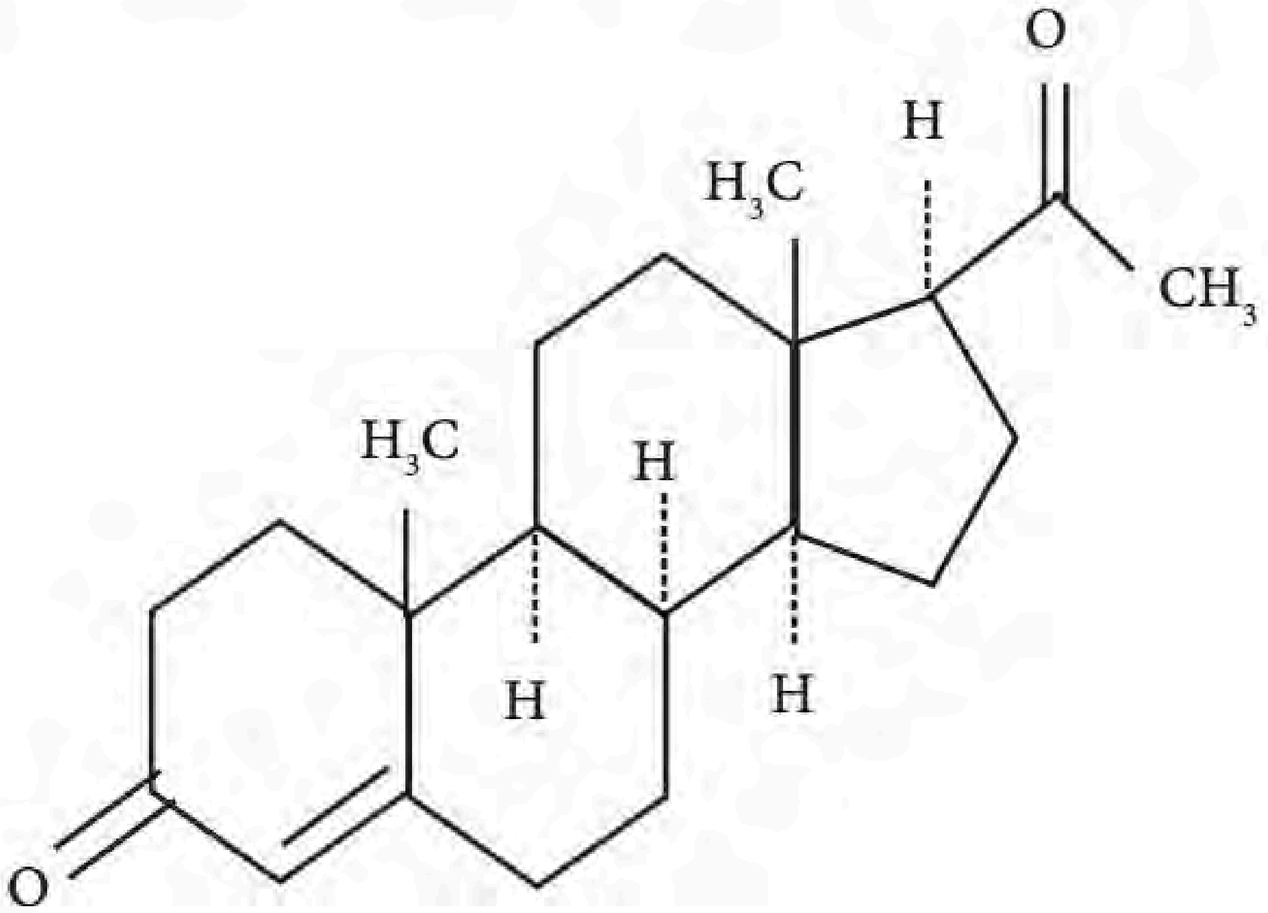
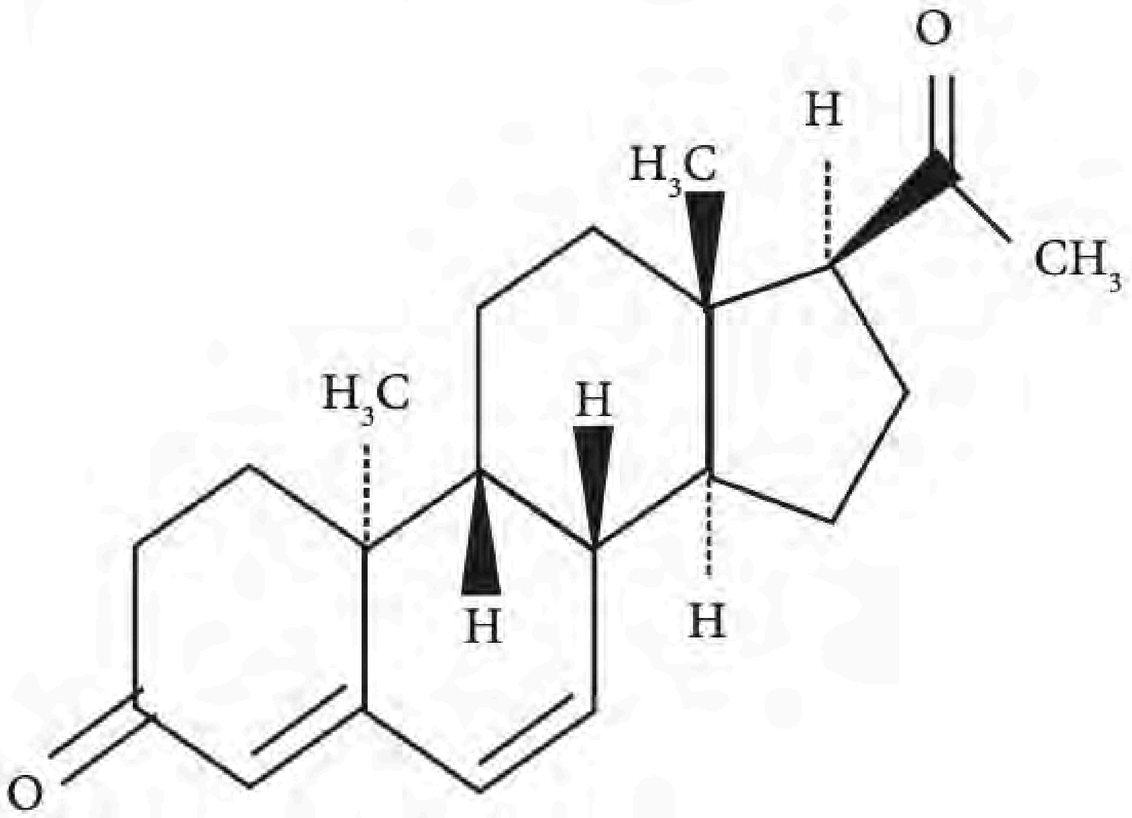


Figure 2. Structure of Dydrogesterone

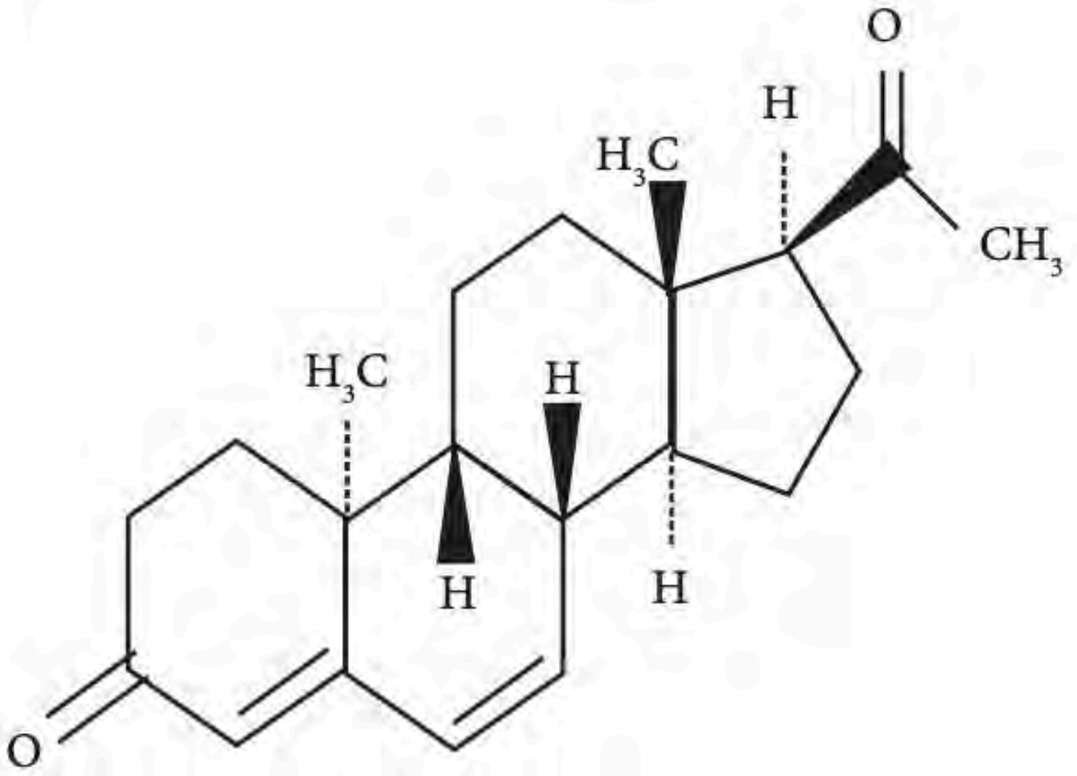


Let’s Get Some Clarity

Clinically available forms of progestOGEN

1. **Medroxyprogesterone acetate (MPA)**
2. **Levonorgestrel**
3. **Norethindrone acetate (NETA) c**

Figure 2. Structure of Dydrogesterone



4.Progesterone: How Should I Prescribe It?

Progesterone Therapy Options:

- Oral Progesterone
- Progesterone Suppositories
- Transdermal Progesterone Cream

Progesterone: How Should I Prescribe It?

Perimenopausal Women:

Low-dose continuous oral micronized

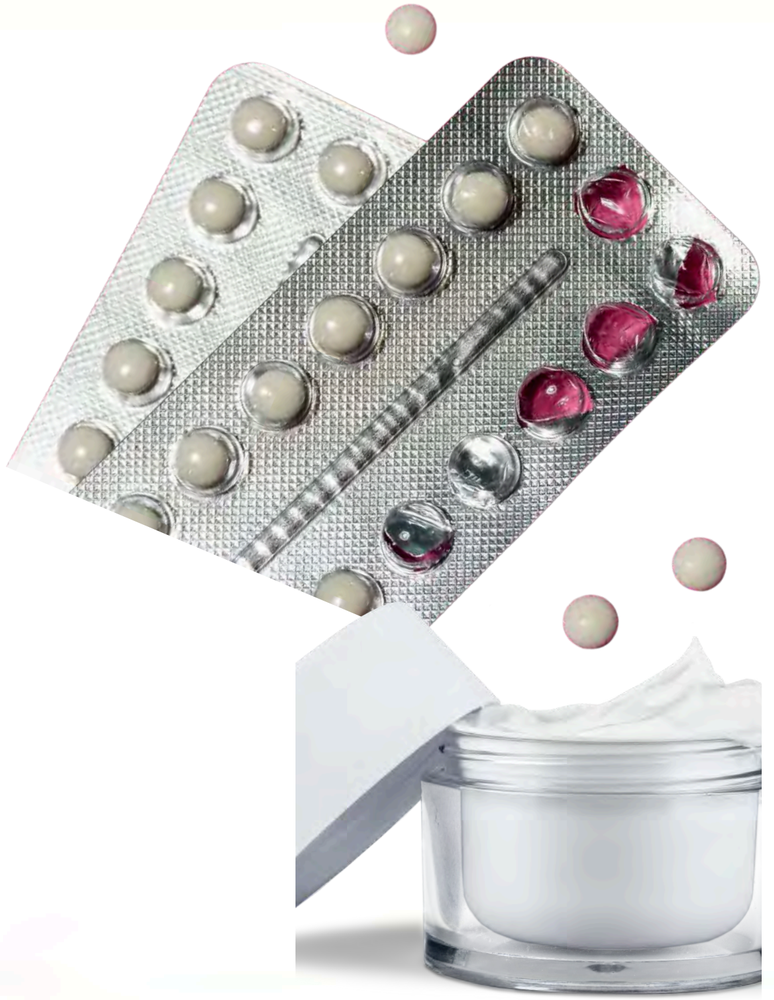
- Start at 25mg QHS and titrate up until symptoms resolve

Low-dose cyclical during the luteal phase

- Start at 12.5mg or 25mg QHS

Menopausal Women:

- Start 75mg - 100 mg continuous low-dose oral micronized (increase as needed to resolve symptoms)
- Continuous low dose with a cyclical dose increase for 7-14 days of oral micronized
- Start at 75mg of transdermal dosing via cream (may have to instruct to use multiple times a day).



What are the Side Effects of Continuous Progesterone?

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Hormone therapy and risk of myocardial infarction: a national register study

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Aim To assess the risk of myocardial infarction (MI) as a result of hormone therapy (HT), with focus on the influence of age, duration of HT, various regimens and routes, progestagen type, and oestrogen dose.

Methods and results All healthy Danish women (n = 698 098, aged 51–69) were followed during 1995–2001. On the basis of a central prescription registry, daily updated national capture on HT was determined. National Registers identified 4947 MI incidents. Poisson regression analyses estimated rate ratios (RRs). Overall, we found no increased risk [RR 1.03 (95% CI: 0.95–1.11)] of MI with the current HT compared with women who never used HT; age-stratified RR among women aged 51–54, 55–59, 60–64, and 65–69 years were 1.24 (1.02–1.51), 0.96 (0.82–1.12), 1.11 (0.97–1.27), and 0.92 (0.80–1.06), respectively. An increasing risk with longer duration was found for younger women, which was not observed with older age groups. In all age groups, the highest risk of MI was found with continuous HT regimen. No increased risk was found with unopposed oestrogen, cyclic combined therapy, or tibolone. Significantly lower risk was found with dermal route than oral unopposed oestrogen therapy (P = 0.04). No associations were found with progestagen type or oestrogen dose.

Conclusion In a National cohort study, we found that HT regimen and route of application could modify the influence of HT on the risk of MI.

Keywords Hormone therapy • Hormone replacement therapy • Myocardial infarction • Coronary heart disease • Ischaemic heart disease • Oestrogen

Background

Postmenopausal use of hormones was widely used in the western world until 2002, when the largest randomized clinical trial (RCT), the Woman's Health Initiative (WHI), investigating the health effects of continuous combined hormone therapy (HT) was prematurely terminated due to overall increased morbidity with HT.[1] This finding was unexpected, as a primary preventive effect of HT on cardiovascular diseases was predicted to outbalance the perceived increased risk of breast cancer and venous thrombo-embolism. These expectations were based on observational studies;[2] however, the WHI found an increased risk of both coronary heart disease and stroke.[1,3] These findings were in accordance with an earlier RCT that tested the effect of HT on re-event after coronary heart disease (the HERS study[4]).

Following the study termination, part of the WHI testing unopposed oestrogen vs. placebo among women without uterus was also prematurely stopped, as no cardio-protective was observed, and an increased risk of stroke was instead found.[5] The discrepant findings from the RCT and observational literature were the topic of much debate. The observational studies could be influenced by a 'healthy user' bias,[2] and the WHI was criticized for not being applicable for healthy younger perimenopausal women.[6,7] Recently, the RCT and observational results have been found to be more in agreement if time since HT initiation was controlled for these studies was found to be in closer agreement.[8]

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Micronized Progesterone and Transdermal Estradiol Can Help with Depression

JAMA Psychiatry | Original Investigation

Efficacy of Transdermal Estradiol and Micronized Progesterone in the Prevention of Depressive Symptoms in the Menopause Transition

A Randomized Clinical Trial

Jennifer L. Gordon, PhD; David R. Rubinow, MD; Tory A. Eisenlohr-Moul, PhD; Kai Xia, PhD; Peter J. Schmidt, MD; Susan S. Girdler, PhD

IMPORTANCE The menopause transition and early postmenopausal period are associated with a 2- to 4-fold increased risk for clinically significant depressive symptoms. Although a few studies suggest that hormone therapy can effectively manage existing depression during this time, to our knowledge, there have been no studies testing whether hormone therapy can prevent the onset of perimenopausal and early postmenopausal depressive symptoms.

OBJECTIVE To examine the efficacy of transdermal estradiol plus intermittent micronized progesterone (TE+IMP) in preventing depressive symptom onset among initially euthymic perimenopausal and early postmenopausal women. A secondary aim was to identify baseline characteristics predicting TE+IMP's beneficial mood effects.

DESIGN, SETTING, AND PARTICIPANTS Double-blind, placebo-controlled randomized trial at the University of North Carolina at Chapel Hill from October 2010 to February 2016. Participants included euthymic perimenopausal and early postmenopausal women from the community, aged 45 to 60 years.

INTERVENTIONS Transdermal estradiol (0.1 mg/d) or transdermal placebo for 12 months. Oral micronized progesterone (200 mg/d for 12 days) was also given every 3 months to women receiving active TE, and identical placebo pills were given to women receiving placebo.

MAIN OUTCOME MEASURES Scores on the Center for Epidemiological Studies-Depression Scale (CES-D), assessed at baseline and months 1, 2, 4, 6, 8, 10, and 12 after randomization, and the incidence of clinically significant depressive symptoms, defined as a CES-D score of at least 16.

RESULTS Of 172 participants, 130 were white (76%), and 70 were African American (19%), with a mean household income of $50 000 to $79 999. The mean age was 51 years, and 43 developed clinically significant depressive symptoms. Women assigned to placebo were more likely than those assigned to TE+IMP to score at least 16 on the CES-D at least once during the intervention phase (32.3% vs 17.3%; odds ratio [OR], 2.5; 95% CI, 1.1-5.7; $P = .03$) and had a higher mean CES-D score across the intervention period ($P = .03$). Baseline reproductive stage moderated the effect of treatment (β, −1.97; SEM, 0.80; P for the interaction = .03) such that mood benefits of TE+IMP vs placebo were evident among women in the early menopause transition (β, −4.2; SEM, 1.2; $P < .001$) but not the late menopause transition (β, −0.9; SEM, 0.3; $P = .23$) or among postmenopausal women (β, −0.3; SEM, 1.1; $P = .92$). Stressful life events in the 6 months preceding enrollment also moderated the effect of treatment on mean CES-D score such that the mood benefits of TE+IMP increased with a greater number of events (β, 1.22; SEM, 0.40; $P = .003$). Baseline estradiol levels, baseline vasomotor symptoms, history of depression, and history of abuse did not moderate treatment effects.

CONCLUSIONS Twelve months of TE+IMP were more effective than placebo in preventing the development of clinically significant depressive symptoms among initially euthymic perimenopausal and early postmenopausal women.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01308814

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Author Audio Interview
Supplemental content

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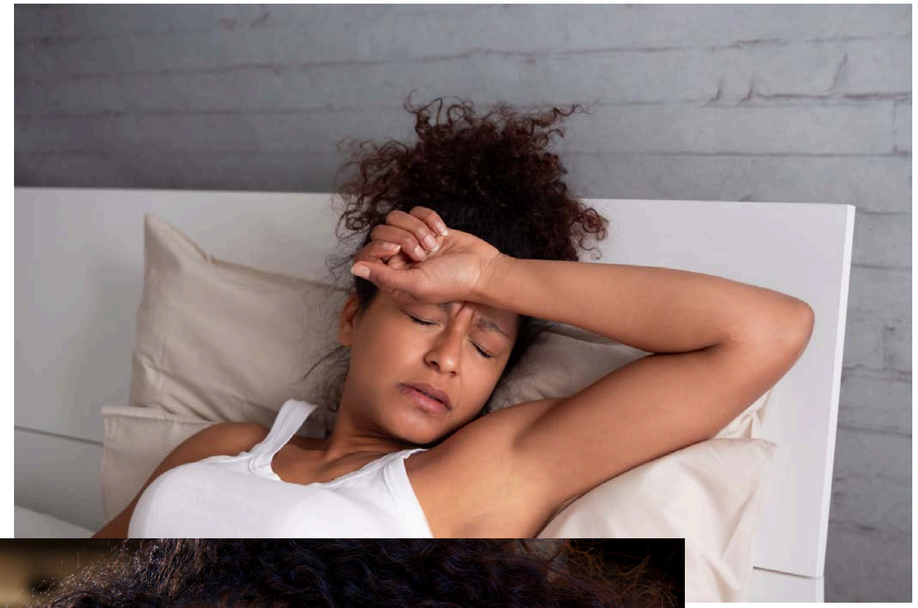
5.What Test Should I Run to Follow Up?

It’s All About the Follow Up

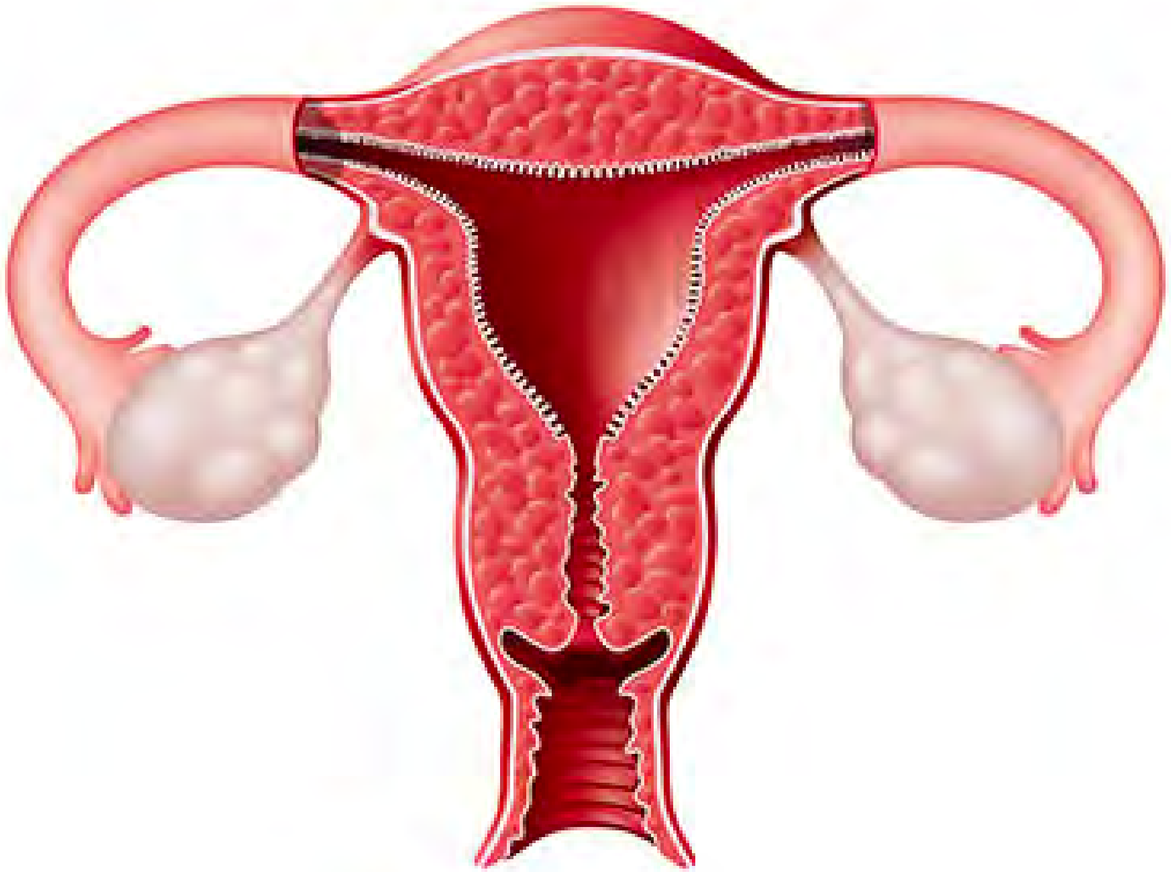
- Serum
- Urine
- Ultrasound to measure the Endometrial Stripe
- Endometrial Bx

6.How Do I Adjust a Patient's Dosing?

Remember, Simply Ask the Patient How She is Feeling.



Get Rid of: “No Uterus, No Progesterone”



The Key Takeaways for the Lecture

- A paradigm shift: Progesterone even when my patient has had a hysterectomy
- Help patients understand that there are different types of progesterone
- Consider continuous progesterone dosing.
- Remember the various ways to test progesterone levels.

Remember

1. **The information in this presentation is provided for informational and educational purposes only and is not medical or treatment advice.**
2. **Any information and statements regarding dietary or herbal supplements have not been evaluated by the Food and Drug Administration and are not intended to diagnose, treat, cure, or prevent any disease.**
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Thank You!