

*Natural Hormone
Replacement: To Meet Each
Woman's Special Needs*

Specialty Compounding Pharmacy

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Purpose

- The purpose of this presentation is to provide information on Natural Hormone Replacement Therapy (NHRT), also called Bio-Identical, and to examine the research to determine its effectiveness in the treatment of peri- and postmenopausal health problems.

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NATURAL HORMONES

- Natural or bioequivalent hormones are obtained from sterol analogues found in many varieties of plants, primarily soybeans and giant Mexican wild yams – **the molecular structure is the same as humans.**
- Censtin ® and Enjuvia ® are both plant derived estrogens and yet they are very similar to premarin (Synthetic estrogen derived from horse urine). The term *natural* in the context of hormone discussions does not necessarily mean that the hormone in question is derived from a source in nature. The term refers to an agent that has a chemical structure identical to that of the hormone molecule produced in the human body. These estrogen and progesterone-like compounds are synthesized in the laboratory to human identical natural hormones.

ESTROGENS Comparison: Is there a difference?

Human Estrogens

- Estrone (E1) 10-20%
- Estradiol (E2) 10-20%
- Estriol (E3) 60-80%

Premarin

- Estrone 75-80%
- Equilin 5-6%
- Estradiol + others 5-19%
- 10 Active estrogens have been identified so far... but there are other compounds and impurities.

BIO-IDENTICAL ESTROGEN FORMULATIONS

Bi-Estrogen (Bi-Est)

- Estradiol (E2) 20%
- Estriol (E3) 80%

Tri-Estrogen (Tri-Est)

- Estradiol (E2) 10%
- Estrone (E1) 10%
- Estriol (E3) 80%

BI-ESTROGEN AND TRI-ESTROGEN

- **Triple estrogen** is a hormone formulation that contains 80% estriol, 10% estrone and 10% estradiol.
 - **Bi estrogen** contains 80% estriol and 20% estradiol.
-
- **Estrone** and the estrogens that convert to estrone in the intestinal tract are thought to be linked to a higher incidence of breast cancer.
 - **Estradiol** is the most potent form of estrogen, and the one produced in the largest amounts by a woman's ovaries before menopause. Estradiol levels fall after menopause. The brand names: Estrace®, Estraderm®, Vivelle®, Alora®, FemPatch™, Estring®, and Climara® contain estradiol.
 - **Estriol** is a weaker estrogen which cannot be converted to estradiol. It is almost completely conjugated in the intestine to glucuronides and sulphates after oral intake; only 1-2% estriol reaches the circulation. Estriol is known as the "weak" or "forgotten" estrogen. Produced in large amounts by the placenta during pregnancy, estriol is also converted in small amounts by the liver. Estriol is not commercially available and possibly the safest estrogen in the U.S., but must be compounded by a pharmacist.
- Estriol, the "weak" estrogen, has been used to manage vaginal dryness, urinary infections, hot flashes, and stress incontinence. The fact that estriol is "weak" has pluses and minuses. Estriol does not provide as much heart and bone protection as other more potent estrogens like estradiol and estrone. But since it has little or no effect for most women on breast or uterine tissue when used in low doses, estriol avoids the risk of breast or uterine cell abnormalities associated with estradiol and estrone.
- Many providers prefer to use these forms of estrogen replacement because they use more estriol and less estrone and estradiol.

Estriol: Safety and Efficacy

- While conventional hormone replacement therapy provides certain benefits, it is not without significant risks.
- Estriol has been found to provide some of the protection without some of the risks associated with stronger estrogens.
- Depending upon the situation, estriol may exert either agonistic or antagonistic effects on estrogen.
- Estriol appears to be effective at controlling symptoms of menopause, including hot flashes, insomnia, vaginal dryness, and frequent urinary tract infections.

Kathleen A. Head, N.D (Alt Med Rev 1998;3(2):101-113)

Estriol: Safety and Efficacy

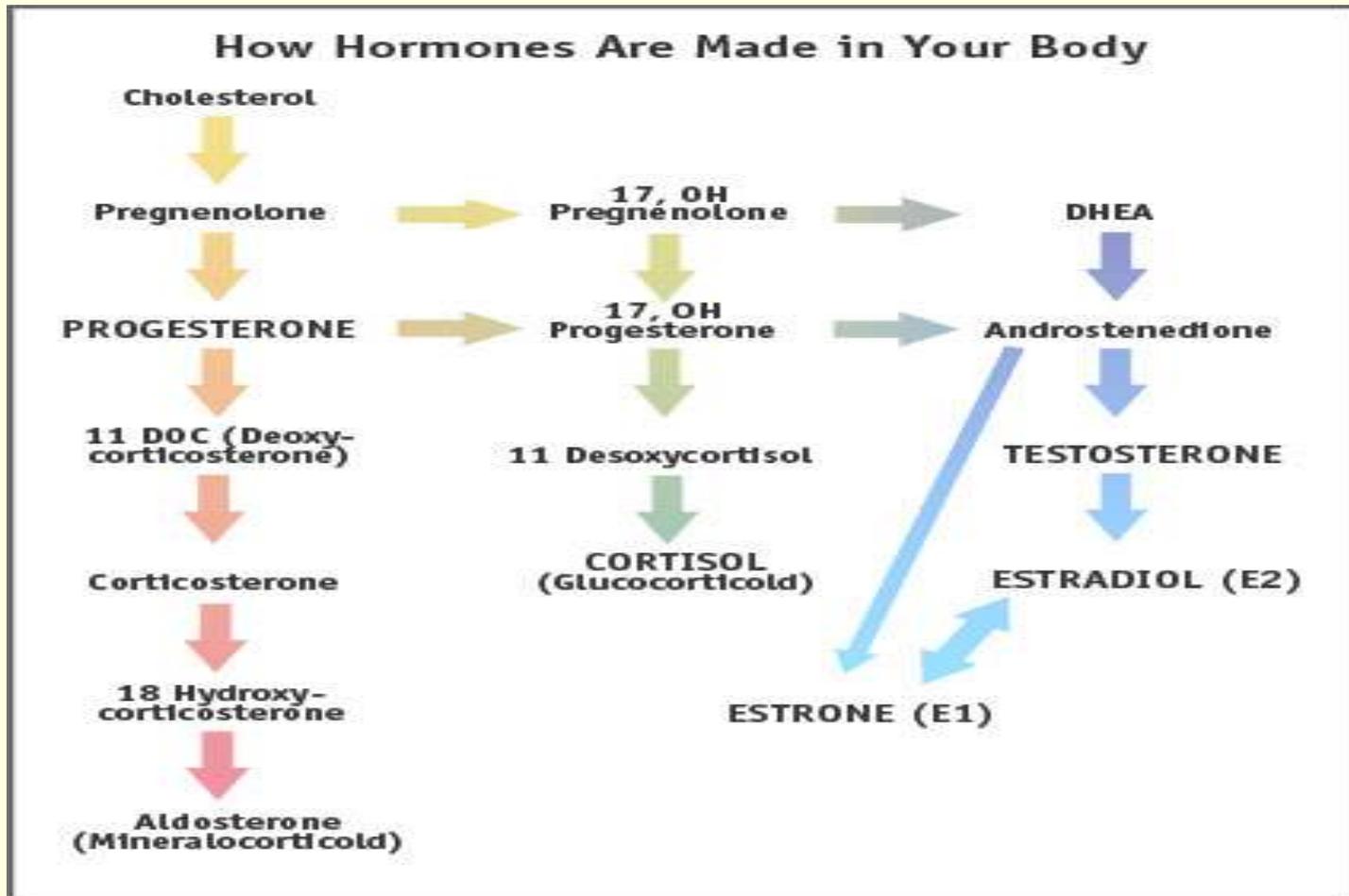
- Research results on estriol's bone density maintaining effects have been contradictory, with the most promising results coming from Japanese studies.
 - All the positive studies on estriol for the prevention of osteoporosis were conducted in Japan. It may be that the Japanese diet, high in phytoestrogens from soy products, potentiates the effect of estriol in this population.

- Estriol's effect on cardiac risk factors has also been somewhat equivocal; however, unlike synthetic estrogen, it does not seem to contribute to hypertension due to the effect on renin activity and aldosterone .

- Although estriol appears to be safer than estrone or estradiol, its continuous use in high doses may have a stimulatory effect on both breast and endometrial tissue.

Kathleen A. Head, N.D (Alt Med Rev 1998;3(2):101-113)

Hormones Pathways



Delivery Systems of Natural Estrogen

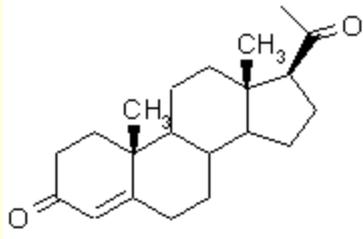
- Oral- immediate or sustained release capsules.
Bi-est or Tri-est 1.25mg-5mg Sublingual- troches or liquids or drops.
- Topical (Transdermal) - creams or gels dosage per ¼ tsp.
- Vaginal- suppositories or cream. Estriol vaginal cream 1-2mg/gm vaginally apply at bedtime.

PROGESTERONES: Not all are alike!

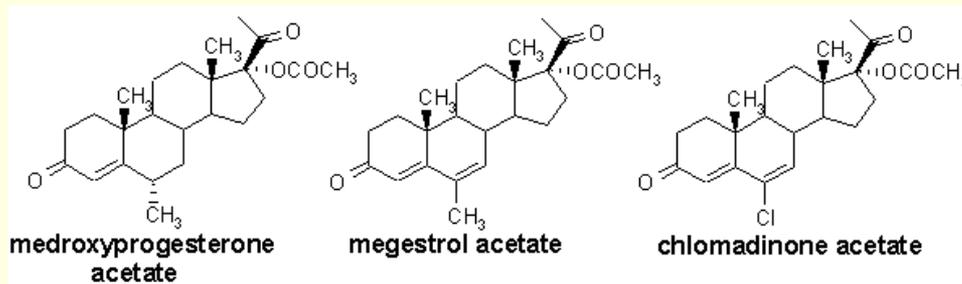
- **Progesterone** is a natural hormone produced by the ovaries.
- **Progestin** refers to the group of synthetic hormones like medroxyprogesterone acetate(MPA) or Provera that have similar actions, but not identical to that of progesterone.
- Synthetic progestins (also called progestogens or progestational agents) are analogues of bio-identical progesterones, and have been developed because they are longer-lasting, more potent, and patentable.
- The synthetic progestins (Provera® was commonly-prescribed synthetic progestin) and similar to the progesterone your body produces, but the subtle chemical differences can significantly influence the hormone's action and side-effects in the body. Synthetic progestins can cause side-effects of irritability, nausea, **depression**, and water retention in some women. Natural progesterone is molecularly identical to the hormone made in the body, and many women find it easier to tolerate.
- The term "*micronized*" refers to the particle size of the progesterone itself.

They may look alike but they are completely different...

■ Progesterone (Natural):



■ Progesterone Synthetic:



PROGESTERONE BENEFITS

- Helps use fat for energy
- Facilitates thyroid hormone action
- Natural antidepressant
- Natural diuretic
- Normalizes blood sugar levels
- Restores proper cell oxygen levels
- Helps restore libido
- Normalizes zinc & copper levels
- Normalizes blood clotting
- Protects against breast fibrocysts
- Provides some protection against breast cancer
- Necessary for survival of embryo
- Stimulates osteoblasts (bone building)
- Precursor for cortiscosterone production (cortisone)
- Necessary for production of nerve myelin

Natural Progesterone Studies

- Synthetic progestins partially negate the beneficial effects on cholesterol levels that result from taking estrogen. (PEPPI Trial).
JAMA, Jan. 18, 1995, 273(3):199-208
- Natural progesterone is effective in raising HDL-cholesterol. In the PEPI trial, natural progesterone was more effective in raising HDLs than the synthetic versions.
- Jerilynn Prior, M.D., of the University of British Columbia in Vancouver, has presented evidence that progesterone can stimulate new bone formation in women with osteoporosis.
 - There may be a role for progesterone use alone or combined with estrogen which reduces bone loss in improving bone mineral density.

Endocrine Reviews 1990, 11(2):386-398 and Canadian Journal of Obstetrics/Gynecology & Women's Health Care 1991, 3:178-84

MPA vs. Bio-identical Progesterone

- Studies at Wake Forest University School Of Medicine have concluded that synthetic medroxyprogesterone (MPA), in contrast to bio-identical progesterone, increases the risk of coronary vasospasm.
- Miyagawa & Frank of Oregon Health Sciences University & USC School of Medicine also compared MPA with natural progesterone as the progestin in HRT and studied the corresponding effect on coronary artery vasospasm. Progesterone + estradiol protected against vasospasm, but MPA + estradiol did not.
- In contrast to some of the synthetic progesterones such as medroxyprogesterone acetate (Provera®, Cycrin®) natural progesterone does not seem to suppress *good* cholesterol (HDL), has no effect on blood pressure or mood, and shows less of a tendency to cause increased male-hormone-like effects such as facial hair growth

Nature Medicine, 3(3):324-7 and *Journal of the American College of Cardiology*, March 1, 1997, pp.671-5

Progesterone Dosage Forms

- **Slow Release Oral Capsule:** 50-400 mg – It combines slow, even-release of medication with the convenience of dosing once or twice daily. The Capsule produces consistent blood levels, which is critical for symptom management in PMS or menopause, and to avoid daytime drowsiness, erratic menstrual cycles or breakthrough bleeding.
- **Micronized Oral Capsules:** 25-200 mg - The capsule is an immediate release form that is taken four times daily. Remember, progesterone is the hormone with a naturally calming effect. Oral forms of natural progesterone may cause drowsiness or dizziness if a woman is taking a dosage strength that is too high for her individual needs. If drowsiness or dizziness occur, the dosage may need to be reduced. Taking natural progesterone with food also helps to avoid drowsiness.
- **Creams or Gels:** 20-100 mg/gm (2-10%) –This is widely dosage form used. Delivers continuous, consistent absorption for symptom management. Progesterone cream is best absorbed when applied to the skin on the hands, but can also be applied to the skin on the stomach, thighs, or inner arms, one to two times a day.

Progesterone Dosage Forms Continued

- **Sublingual Troches:** 50-200 mg – These troches are taken one to 4 times daily, it is used buccally (between the cheek and the gum). It is delivered through mucosal membrane to blood stream, hence bypassing the liver.
- **Suppository:** 25-400 mg - Progesterone suppositories, administered vaginally or rectally contain progesterone in a wax base. They provide consistent, even absorption. When used vaginally, many women complain of leakage that occurs. When used rectally, some patients report bowel stimulation. The lower dosages are most commonly used in treating "luteal phase defects," and higher doses are generally used for treating premenstrual syndrome.
- **Drops:** Oral drops can be used in patients that are in need of quick onset of action or simply on people who need more titrating dosage of the progesterone. For instance the drop can be compounded as little as 1mg/ml for sensitive people that need more adjustments.
- Micronized oral capsules, gels, and creams also work well when combining other hormones with progesterone in the same dosage form.

What to expect....

- Progesterone is a very benign medication that most women tolerate well. Infrequent side-effects may include delay the onset of your period. If this happens and your period is more than a day or two late, you may need to stop taking progesterone to bring on your period, then resume taking it 14 days after your period starts. In addition, you may experience flushing when taking progesterone. This is normal, because progesterone raises body temperature about one degree.

Is it better to take progesterone as a capsule, a shot, a vaginal suppository or a cream?

- All of the above forms of progesterone and progestogens have been used. The method of administration is best determined by availability, convenience of use and price. Absorption and duration of action will vary by the form of progesterone used:
 - pills - peak absorption is about 1-4 hours and is cleared by 24 hours. Taking the pills with food enhances absorption.
 - shots - usually given in the form of progesterone in oil, doses peak at about 12 hours after administration and take at least 48 hours or more to clear.
 - vaginal suppositories, cream - absorbed to peak in 4 hours and cleared by 24 hours.
 - skin creams - creams tend not to absorb through the skin very well but alcohol-based gels are seemed to be more effective.

What are the effects of too little or too much progesterone?

- Progesterone acts to stabilize the tissue lining of the uterus (endometrium) so if it is absent, such as with ovarian anovulation, irregular and heavy menstrual bleeding often occurs after a period without any menstrual bleeding. Thus progesterone is used to prevent this irregularity of bleeding if it is given continuously. If, on the other hand, a onetime bolus of progesterone is given such as with a shot or with only 5 days of oral pills, then the falling progesterone levels will actually cause an estrogen-primed endometrium to slough and therefore start a menses.
- Too much progesterone often causes tiredness and even sedation. This side effect can be beneficial in a women who has epilepsy or even uterine irritability causing preterm labor because progesterone in high doses can decrease seizure activity and uterine contractions.

Does progesterone block or lessen the beneficial effect of estrogen on heart disease and osteoporosis prevention?

- The effect of various estrogen and progestogen/progesterone combinations have been looked at extensively in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial,

Writing Group for the PEPI Trial: Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the postmenopausal estrogen/progestin interventions (PEPI) trial. JAMA 1995;273:199-208.

- Some of the following generalizations can be drawn:
 - high density lipoproteins - basically progestogens such as Provera® lessen some of the estrogen effect of raising HDL (good cholesterol) but in combination with estrogen, the net effect is still to raise HDL a small amount. Natural progesterone does NOT blunt this response and when used with estrogen, HDLs rise more than when Provera® is used.
 - low density lipoproteins - all of the hormone regimen combinations lowered the bad cholesterol (LDL)
 - blood pressure - there were no effects of estrogen alone or any of the combinations with progestogens or progesterone on either systolic or diastolic blood pressure.
 - weight and abdominal girth - interestingly, all women, even those who had no estrogen or progesterone, gained weight and increased abdominal girth during this menopausal study. The women who took *any* hormonal therapy gained LESS weight and had LESS increase in abdominal girth.
 - Blood sugar - all hormonal regimens resulted in a lower fasting blood sugar. However, the estrogen with medroxyprogesterone acetate (Provera®) raised the 2-hour post glucose blood sugar implying that the SYNTHETIC PROGESTERONE may worsen a diabetic tendency.

Androgens

- Androgens, testosterone and dehydroepiandrosterone (DHEA), may be added to ERT to alleviate recalcitrant menopausal symptoms and further protect against osteoporosis, loss of immune function, obesity, and diabetes.
- ERT may represent incomplete preventive hormonal treatment in postmenopausal women because it does not directly address the declines in serum testosterone associated with hysterectomies and age-related gender-independent decline in DHEA and DHEA-sulfate.
- Additionally, ERT may cause relative ovarian and adrenal androgen deficiency, creating a rationale for concurrent physiologic androgen replacement.

Obstetrics & Gynecology 1997-90(6):995-8

Testosterone

- In men, TESTOSTERONE is primarily produced in the testes and to a lesser extent in the adrenal glands. In women, testosterone is produced in the ovaries, adrenal glands and to a lesser extent in the skin, brain and liver.
- Testosterone may increase levels of estrogen in some men and women which is not always desirable. The "methyl" form is less likely to be converted to estrogen and is better absorbed. Liver function must be monitored more closely.
- Testosterone can be the "Impulsive Hormone," and there is a parallel of information about it in men and women. Those with higher levels are usually single, aggressive, and dominate and take risks, but these impulses can be channeled and controlled in order to avoid problems. In women a little bit can go a long way, as it enhances sexual desires and fantasies, helps make women more easily sexually aroused, to enjoy intercourse better and have more frequent orgasms.

Testosterone Usage

- If you have your ovaries removed or you are in natural menopause, your testosterone levels drop by 1/3 or more, and it is definitely advisable to replace it along with estrogen. As one author, Dr. Susan Rako, MD, stated, "It is the Hormone of Desire." Besides the bone and sexual benefits, it also acts on the brain, muscles, liver and blood vessels, as it enhances cognitive functions.
- Testosterone can be administered in sublingual troches, as a single testosterone dose or in combination with progesterone and estrogens.

Forms and dosages of testosterone supplementation include:

- The sublingual troche is usually placed between the cheek and the gum about 2 hours prior to bedtime.
- A topical gel that in a unique hydro alcoholic vehicle to obtain the maximum absorption.
- A testosterone 2% ointment is commonly prescribed at the same time with the topical gel to be used as a boost. A small amount (lentil pea size) is applied to vulva area about 1 hour prior to bedtime every night for 3-4 weeks.

Estrogen plus Progesterone Combined

- Triest 2.5mg Progesterone 5% Gel.
This is the most widely used mixture. The patients apply $\frac{1}{4}$ tsp twice a day. It can easily be adjusted by applying $\frac{1}{4}$ tsp AM or $\frac{1}{2}$ tsp PM, or simply lowering the dosage into half by apply $\frac{1}{8}$ tsp Twice a day.
- For those patients that like taking the capsules over topical applications based on their symptoms and blood level the following are commonly prescribed:

Triest 2.5mg one capsule twice a day combined with progesterone 50mg one capsule in the morning and 2 capsules at bedtime.

Key To Hormone Symptoms Evaluation

Breast Tenderness	↑E	↓P	↑P				
Sleep Disturbances/Insomnia	↓P	↓E	↑T				
Cramps	↓P						
Fluid Retention	↓P	↑E					
Breakthrough Bleeding	↓P						
Fatigue	↓T	↓TH	↑P	↓C			
Loss of Memory	↓T	↓E					
Bladder Symptoms	↓E	↓T					
Arthritis	↓T	↓P					
Harder to Reach Climax	↓T	↓E	↓P				
Decreased Sex Drive	↓T	↑E	↓C	↓TH			
Hair Loss	↑T	↑↓TH	↓↑E	↓↑P			

Fibrocystic Breast	↑E	↓P					
Weight Gain	↑E	↓P	↓TH				
Heavy/Irregular menses	↑E	↓P					
Hot Flashes	↓E	↑↓E	↓P				
Dry Skin/Hair	↓E						
Anxiety	↑E	↓P	↓E				
Depression	↓E	↑P	↓T	↑C	↓T		
Night Sweats	↓E	↑↓C					
Vaginal Dryness	↓E	↓T					
Headaches	↑↓E	↑↓P	↓T	↓TH			
Irritability	↑E	↑↓P					
Mood Swings	↑E	↓P					

E=Estrogen P=Progesterone T=Testosterone C=Cortisol TH=Thyroid

↑=Caused by High Level ↓=Caused by Low Level ↑↓=Caused by Fluctuating Levels

Represents the most common causes of symptoms, as far as Progesterone, Estrogen, Testosterone and Thyroid only, and is not totally inclusive of all possible causes.