



Secundum Artem

*Current & Practical Compounding
Information for the Pharmacist.*

COMPOUNDING FOR HORMONE REPLACEMENT THERAPY

INTRODUCTION

In the year 2000, an estimated 20 million women will become menopausal in the United States.¹ In the lives of many women, this is a life-changing event leading to requests for assistance, understanding, a sympathetic ear and treatment for some of the symptoms associated with this change.

The routine prescription for conjugated equine estrogens and medroxyprogesterone acetate fails to take the individual needs, backgrounds and lifestyles into consideration.² In many cases, women are offered a standard brand, one-size-fits-all therapy when medical care is sought for both the physical and emotional symptoms associated with these hormonal changes occurring in the woman's body. With managed care restraints on the time health practitioners can spend with patients, these women are not receiving the care they need and to which they are entitled. With more prescriptions being written for Premarin than for any other medication in the United States, the market is obviously present for hormone replacement therapy. This is also supported by the recent activities among pharmaceutical companies to market their own brands of conjugated estrogens.

Individualization of patient care rather than mass treatment is one issue here. The question is, what degree of individualization of care is really needed? What can be provided? Who can provide it? Another question to answer is whose decision is it...the patient's, her health care provider's or the third-party payer's?

As the baby boomers (born during WW II) move into mature adulthood, this area will no doubt continue to increase in importance. We are presenting this issue for the support of quality compounding of natural hormone replacement preparations.

DEFINITIONS AND ABBREVIATIONS

ERT is estrogen replacement therapy and involves treatment using a number of different estrogens that are available. HRT is hormone replacement therapy and involves a combination of hormones, including estrogens, progestins and even androgens.

Natural (bio-identical) hormones refer to those hormones that are molecularly identical to those made in the human body and have the same exact chemical structure.

Plant-derived refers to those hormones that are chemically derived from precursors found in yam or soy plants. Chemically, they will have the same chemical structure as those that are

totally synthesized.

Synthetic (Patented, Conventional, Artificial) hormones are those that are not usually found in humans and are chemically different from the naturally occurring human hormones. They are not identical in structure or activity to the natural hormones they are designed to emulate.

The Natural Hormones include estrone (E1), estradiol (E2), estriol (E3), progesterone, testosterone, dehydroepiandrosterone, pregnenolone and androstenedione. In humans, the estrogens are primarily composed of 10-20% estradiol (E2), 10-20% estrone (E1), and 60-80% estriol (E3). For comparison, Premarin® is composed of 5-19% estradiol (& others), 75-80% estrone and 6-15% equilin.

THE MENSTRUAL CYCLE

In a woman's life, between puberty and menopause, the menstrual cycle is somewhat regular and predictable and can be divided into about 7 phases, each lasting the approximate number of days as indicated in Table 1. During the different phases of the cycle, there is a constant changing of the quantity of estrogens, progesterone, LH and FSH in the body.

The estrogens are responsible for normal growth and development of female sex organs, maintenance of secondary sex characteristics, promoting the proliferation and growth of specific cells in the body, protection against bone loss and protection against heart disease.

Progesterone (1) is important for promoting secretory changes in uterine endometrium (counteracting the prolific action of the estrogens), (2) is necessary for maintaining pregnancy (maintains the uterine lining and decreases uterine contractions), (3) prepares the breasts for lactation, stimulates osteoblast-mediated new bone formation (increases bone mass and density) and, (4) is metabolized to other active hormones.

Testosterone serves to enhance libido, provides cardiovascular protection (lowers cholesterol), enhances bone building (increases calcium retention) and improves the energy level and mental alertness.

Estrogens, progestins and androgens are important endogenous hormones that produce numerous physiological actions. Their

presence is necessary for normal development and maturity. As one emerges from childhood to adolescence, these hormones are responsible for many of the physiological changes that occur to prepare one for adulthood. Throughout one's adult life, these hormones are usually kept in balance but may be modified through the administration of additional hormones, as in the case of contraception. Nonetheless, adult life is generally characterized by the presence of circulating levels of these hormones.

As one continues to mature into the fifth decade or so of life, these hormones generally start decreasing in prevalence and changes in the adult body begin to occur to prepare one for mature adulthood. These changes generally involve a decrease in these hormones leading through a change in life termed the menopause. While most think of menopause as related to women, there are also changes in the male at about the same time in life.

The symptomatology associated with these changes is uncomfortable for many patients and they seek medical help. Since the hormones the body has been producing and responding to generally involve estradiol, estriol, estrone, progesterone and testosterone, these are termed "natural" and their replacement is termed "natural hormone replacement therapy". This is compared to the administration of other estrogens, progestins and androgens that are commercially available that are chemically modified products, even though they may actually come from natural animal (nonhuman) sources. As the natural hormones are not patentable substances, there has been little historical interest from the pharmaceutical industry in promoting their use. However, as compounding pharmacists, this provides opportunities for meeting patient needs on an individual basis.

THE STAGES OF A WOMAN'S LIFE

A woman's life can be divided into four different stages as it relates to menopause.

1. Premenopause occurs at the onset of the first menstrual period and is characterized by routine fluctuations of estrogens, progesterone, luteinizing hormone and follicle stimulating hormone.
2. Perimenopause occurs between the onset of changes in the hormonal secretions and the onset of menopause. There are fluctuating hormonal secretions due to intermixed normal and abnormal menstrual cycles. This is also called the period of estrogen dominance.
3. Menopause occurs at the termination of the menstrual periods and is defined as missing twelve consecutive periods. It should be noted that not all women experience problems associated with menopause.
4. Postmenopause is the period of time following the last menstruation. During this time, HRT can be used to aid in heart protection, improve the lipid profile and enhance bone mass.

SIGNS AND SYMPTOMS OF MENOPAUSE

The reduction of endogenous estrogens and progestogens after menopause results in a variety of vasomotor symptoms in women. These often experienced signs and symptoms of menopause are listed in Table 2 (Symptoms associated with a decrease in estrogen) and Table 3 (Symptoms associated with a decrease in progesterone). Menopause is not an illness, but a natural occurrence in a woman's life that may lead to increased risks, including heart disease, specifically, myocardial infarction and angina. Osteoporosis is another major health problem as well as vaginal atrophy and Alzheimer's disease.

TREATMENT

The treatment of menopause is, to some degree, seeking an elusive answer to hormone imbalance. The patient and health care provider is, in many cases, seeking a simple answer to a complex problem, or set of symptoms. One simple answer generally does not exist. A few general rules can be stated related to hormone replacement therapy.

1. There is no simple answer or single approach to HRT.
2. Treat each patient as an individual.
3. HRT may be difficult and is time consuming.
4. Generally, one cannot successfully treat hormone imbalances with hormones alone.

The decision to use HRT is an individual one, based on the individual's particular risks. The goals of natural HRT are to (1) alleviate the symptoms caused by the natural decrease in production of hormones by the body, (2) replace the hormones to the extent to provide positive benefits, (3) bring the body back to normal hormonal balance, and (4) imitate the body's natural processes as much as possible.

The natural aging process results in a decrease in selected hormone levels in the body. These natural hormones are made by the body and have contributed to survival and longevity throughout the life span of the human race. These hormones are not dangerous and have not subjected women to disease and it is not likely that we will develop a better synthetic drug to take their place. Consequently, it only makes sense to provide back to the body the exact chemical hormones to replace the lower levels that occur as a result of menopause.

The benefits of natural HRT include (1) minimizing symptoms of menopause prevention of osteoporosis, (2) improved lipid profiles, (3) reduced risk of heart disease, (4) reduced risk of endometrial and breast cancer, and (5) prevention of Alzheimer's disease.

HORMONES AND DOSING

Postmenopausal dosing guidelines vary with the patient and what is presented is only a guide. Each patient must be individually assessed, dosed and followed. Dosing of Double Estrogens or Triple Estrogens is generally in the range of 0.625 to 5 mg given once or twice daily. Progesterone is usually dosed in the range of 25 to 200 mg daily. Testosterone is often dosed in the range of 0.25 to 2 mg daily. Obviously, these doses can be lowered or raised based upon the response of the patient and the dosage form that is used. The Double Estrogen mixture consists of 80% estriol and 20% estradiol. The Triple Estrogen mixture consists of 80% estriol, 10% estrone and 10% estradiol.

Various routes of administration are used, including oral, transdermal, nasal, vaginal, sublingual, buccal and others. In the oral administration of capsules, the release rate of the hormone is often retarded by the use of a cellulose polymer that forms a gel when the capsule shell dissolves. The gel slowly releases the hormone over a few hours and this minimizes high peaks that may occur when a lactose filler is used and the drug is rapidly released.

Transdermal delivery of hormonal steroids offers a number of advantages over other modes of administration; it normally allows the use of small amounts of the hormone for a long-lasting effect by avoiding chemical or metabolic degradation of drugs that may occur in the gastrointestinal tract. Moreover, by bypassing the liver, transdermal delivery eliminates the potential drawbacks associated with hepatic steroid metabolism.³ However,

er, the absence of wide-range controlled studies to monitor the pharmacokinetics and biological effects of transdermal progesterone application in the general population makes it important to monitor the patients on a routine basis.

Estradiol is a naturally occurring steroidal estrogen that occurs as white or creamy white, small crystals or as a crystalline powder. It is odorless, hygroscopic and is practically insoluble in water but has a solubility of about 35.7 mg/mL in alcohol at 25°C. It should be stored in tight, light-resistant containers. In the body, estradiol is reversibly oxidized to estrone and both estradiol and estrone can be converted to estriol. Generally, estradiol is not used orally due to extensive first-pass hepatic metabolism. Estradiol is indicated in the treatment of atrophic vaginitis, atrophic dystrophy of vulva, menopausal symptoms, female hypogonadism, ovariectomy, primary ovarian failure, inoperable breast cancer, inoperable prostatic cancer and mild to severe vasomotor symptoms associated with menopause.^{4,6}

Estriol is a naturally occurring estrogen and is claimed to have a selective action on the cervix, vagina and vulva and to have relatively little effect on the endometrium. It is often given in combination with estrone and estradiol in estrogen replacement therapy. It is a crystalline powder that is practically insoluble in water but is soluble in alcohol and vegetable oils. In the body, estradiol is reversibly oxidized to estrone and both estradiol and estrone can be converted to estriol.^{6,7}

Estrone is a naturally occurring steroidal estrogen prepared either from the urine of pregnant mares or from the Mexican yam (*Dioscorea*). It occurs as small, white crystals or as a white to creamy white, crystalline powder that is odorless and is practically insoluble in water. It is soluble to the extent of 4 mg/mL in alcohol and is soluble in vegetable oils. In the body, estradiol is reversibly oxidized to estrone and both estradiol and estrone can be converted to estriol. Estrone is used in the treatment of hypogonadism, primary ovarian failure, vasomotor symptoms of menopause, prostatic carcinoma, inoperable breast cancer, kraurosis vulvae, and abnormal uterine bleeding due to hormone imbalance.^{4,6}

Progesterone is a naturally occurring progestin that occurs as a white or creamy white, crystalline powder that is practically insoluble in water, soluble in alcohol, sparingly soluble in vegetable oils, and exists as a polymorph that melts at 121°C. Progesterone is extensively metabolized by the liver and is not usually given by the oral route, with some exceptions. Store in tight, light-resistant containers.^{4,8}

Testosterone occurs as white or slightly creamy white crystals or crystalline powder that is odorless and stable in air. It is practically insoluble in water, soluble 1 g in 5 mL of ethanol, 2 mL of chloroform and 100 mL of ether. It is soluble in vegetable oils. It melts between 153 and 157°C. Testosterone is subject to photodegradation in the presence of light. Testosterone is not very bioavailable when given as an oral-swallow preparation, but it is absorbed when administered buccally and sublingually. The different esters of testosterone are hydrolyzed to free testosterone and, subsequently, are metabolized in the same way as testosterone itself. Testosterone is indicated as androgen replacement for delayed male puberty, postpartum breast pain and engorgement, inoperable breast cancer and male hypogonadism.^{4,6,8}

SIDE EFFECTS OF THERAPY

Side effects of HRT are listed in Table 4 and can often be mini-

mized by alteration of the dose. It is important to determine if the side effects are estrogen or progesterone related and an appropriate adjustment made. With each dosage adjustment, sufficient time should be allowed for patient response before another adjustment.

PATIENT COUNSELING

Inherent in the success of treating menopausal patients is taking the time for thorough education, which starts with patient assessment. One must know the patient's history and the family history (presence of breast cancer, cardiovascular disease or osteoporosis). Individual files should be maintained on each patient.

Dietary recommendations are important and should include reduced fat and plenty of fresh vegetables, legumes and whole grains. Another important component is exercise, which helps in building stronger bones, increases the immune system function, decreases depression and anxiety and can actually reduce many symptoms of premenstrual syndrome and menopause.

MARKETING HRT

Education programs can be provided to doctors and nurses as well as to the lay public. Promotional materials concerning educational programs can be provided to places where women gather. Formal or informal seminars have been very successful in presenting the topic. Pharmacists providing these seminars generally begin with a short story of their pharmacy, the importance and legal aspects of compounding, the purposes of estrogens, progestins and androgens, compliance issues and compensation and insurance billing. These are often followed up by one-on-one personal consultations. After a personal consultation, many pharmacists follow up with a communication to the physician and/or nurse by telephone or fax.

PATIENT FILES

A consultation is an excellent way to start the process of patient history review and the use of a symptoms chart. In addition, laboratory test values can be maintained in this chart. While laboratory tests such as serum levels, saliva levels and urine monitoring have their place in patient evaluation, they do have limitations. However, using laboratory analysis in combination with clinical observation pharmacists can better recommend starting doses and dosage adjustments of hormone replacement for patients. The symptoms chart characterizes symptoms of estrogen excess, estrogen deficiency, progesterone excess and progesterone deficiency. This chart can be used during an initial patient consultation to determine a woman's supplemental hormonal needs and then again on subsequent visits to determine if the woman's prescribed dosages are meeting or exceeding her hormone requirements. The symptoms list chart is a tool which can be used to evaluate patients for their starting hormone dosages and a tool that can be used to evaluate the effectiveness of current hormone regimes. Pharmacists wishing to help women with their hormone needs should use all available tools including but not limited to family history evaluation, symptoms list chart, serum or saliva levels, bone density monitoring and uterine lining monitoring to completely assess the needs of their patients.

MOST COMMONLY COMPOUNDED HRT PREPARATIONS

There are numerous HRT formulations being compounded today. Among the most common are Progesterone Capsules, Progesterone Topical Creams, Testosterone Topical Creams, Triple Estrogen Capsules, Triple Estrogen with Progesterone Capsules, Progesterone Slow Release Capsules, Progesterone Vaginal Suppositories, Triple Estrogen with Progesterone and Testosterone Capsules, Progesterone in a Pluronic-Lecithin Organogel, Double Estrogen Capsules, Progesterone Troches, and Testosterone Capsules.

FORMULATIONS

Rx Double Estrogen 2.5 mg Capsules (Estriol 2 mg, Estradiol 0.5 mg)

Estriol	200 mg
Estradiol	50 mg
Lactose OR	39.75 g
Starch OR	37.25 g
Methocel E4M with	10 g
Lactose	23.75 g

Procedure for the above capsules (Each formula is for 100 #1 capsules)

1. Blend the estriol and estradiol powders together.
2. Geometrically, incorporate the lactose or starch and mix thoroughly, OR
3. Geometrically, incorporate the Methocel E4M, then the lactose and mix thoroughly.
4. Encapsulate 100 capsules, using a size #1 capsule.
5. Check the weights of at least 10 capsules.
6. Package and label.

Rx Triple Estrogen 2.5 mg Capsules (Estriol 2 mg, Estrone 0.25 mg, Estradiol 0.25 mg)

Estriol	200 mg
Estrone	25 mg
Estradiol	25 mg
Lactose OR	39.75 g
Starch OR	37.25 g
Methocel E4M with	10 g
Lactose	23.75 g

Procedure for the above capsules (Each formula is for 100 #1 capsules)

1. Blend the estrone and estradiol powders together.
2. Incorporate the estriol and mix well.
3. Geometrically, incorporate the lactose or starch and mix thoroughly OR
4. Geometrically, incorporate the Methocel E4M, then the lactose and mix thoroughly.
5. Encapsulate 100 capsules, using a size #1 capsule.
6. Check the weights of at least 10 capsules.
7. Package and label.

Rx Triple Estrogen 2.5 mg, Progesterone 100 mg and Testosterone 1 mg Capsules

Estriol	200 mg
Estradiol	25 mg
Estrone	25 mg
Progesterone	10 g
Testosterone	100 mg
Lactose	32.5 g (#1 capsule)

Procedure for the above capsules (Each formula is for 100 #1 capsules)

1. Mix the estradiol and estrone powders thoroughly.
2. Incorporate the testosterone powder.
3. Incorporate the estriol powder.
4. Incorporate the progesterone powder and mix.
5. Incorporate the lactose and thoroughly mix.
6. Encapsulate 100 capsules using a size #1 capsule.
7. Check the weights of at least 10 capsules.
8. Package and label.

Rx Progesterone 5% Cream

Progesterone, micronized	5 g
Glycerin	qs
Dermabase	95 g

Procedure:

1. Levigate the micronized progesterone with a small quantity of glycerin to form a smooth paste.
2. Geometrically, incorporate the Dermabase and mix until uniform and smooth.
3. Package and label.

Rx Progesterone 200 mg/mL in Pluronic Lecithin Organogel

Progesterone, Micronized	20 g
Propylene Glycol	20 mL
Lecithin:Isopropyl Palmitate Solution*	20 g
Pluronic F127 20% Gel** qs	100 mL

Procedure:

1. Prepare a paste of the micronized progesterone and the propylene glycol.
2. Add the Lecithin:Isopropyl Palmitate Solution and mix well.
3. Add sufficient pluronic F127 20% gel to volume and mix well.
4. Package and label.

*The Lecithin: Isopropyl Palmitate Solution can be prepared by mixing 10 g of soy lecithin and 10 g of Isopropyl palmitate; allow to stand overnight for complete dissolution to occur.

**The Pluronic F127 20% Solution can be prepared by adding 20 g of pluronic F127 to sufficient cold (ice) water to make 100 mL. For complete dissolution, place in a refrigerator and allow to stand with periodic agitation.

Table 1. The phases of the menstrual cycle.

<u>Days</u>	<u>Phase</u>	<u>Hormonal Levels</u>
1-4	Menstruation	Rising estrogen levels
5-8	Postmenstruum	Peaking estrogen levels
9-12	Late postmenstruum	Falling estrogen levels
13-16	Ovulation	Low estrogen levels
		Peak follicle stimulating hormones (FSH)
		Peak luteinizing hormones (LH)
17-20	Post ovulation	Rising estrogen and progesterone levels
21-24	Early premenstruum	Peak estrogen and progesterone levels
25-28	Premenstruum	Falling levels of estrogen and progesterone

Table 2. Symptoms associated with a decrease in estrogen.

- Anxiety
- Dry skin
- Heart palpitations
- Inability to reach orgasm
- Memory loss
- Night sweats
- Shortness of breath
- Vaginal dryness
- Yeast infections
- Depression
- Headache
- Hot flashes
- Lack of menstruation
- Mood swings
- Painful intercourse
- Sleep disorders
- Vaginal shrinkage

Table 3. Symptoms associated with a decrease in progesterone.

- Acne
- Anxiety
- Cramps
- Early menstruation
- Food cravings
- Headache
- Insomnia
- Low libido
- Painful breasts
- Swollen breasts
- Asthma
- Bloating
- Depression
- Emotional swings
- Fuzzy thinking
- Inability to concentrate
- Irritability
- Moodiness
- Painful joints
- Weight gain

Table 4. Side effects associated with HRT.

- Bloating
- Craving for sweets
- Fatigue
- Heavy/irregular menses
- Loss of sex drive
- Pounding headache, bilateral
- Recurrent vaginal yeast infections
- Vomiting
- Weight gain
- Breast enlargement and tenderness
- Depression
- Fibrocystic breasts
- Leg cramps
- Nausea
- Premenstrual-like mood swings
- Thinning of the hair
- Water retention
- Yellow-tinged skin

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