Dr. Cullinan provides a current and in-depth review of the use of ultrasonography in the gynecologic evaluation of the menopausal woman, and Drs. Lalonde and Daniell explore various modes of treatment for abnormal uterine bleeding in menopause. In the absence of definitive answers as to the appropriate hormone replacement in women who are surgically treated for endometriosis with total abdominal hysterectomy bilateral salpingoophorectomy, Dr. Molpus makes an excellent case for including progestational agents in these women's hormone replacement regimen to prevent recurrence of endometriosis.

Finally, the theoretic and real effects of estrogen therapy that mediate the cardiovascular benefit associated with menopausal hormone replacement are reviewed by Drs. Vendola and Simon. The risks and benefits of the various components of hormone replacement regimens are examined by Dr. Orhan and myself, leading to the conclusion that it is the rare postmenopausal woman who does not benefit from hormone replacement with regard to quality of life.

Therapeutic issues in the management of menopausal woman that are often encountered by the practicing reproductive endocrinologist and the general gynecologist have been addressed in this *Clinics* issue from both a physiologic and practical perspective. Hopefully as our understanding of the aging process increases, the care provided to aging women will be enhanced. It is to this end that this issue is dedicated.

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AN ALTERNATIVE METHOD OF HORMONE REPLACEMENT THERAPY USING THE NATURAL SEX STEROIDS

Joel T. Hargrove, MD, and Kevin G. Osteen, PhD

When ovarian function is lost by surgical removal, chemotherapy, irradiation, autoimmune disease, or by the natural menopause, there is a marked decline in the circulating levels of sex steroids. The three types of these steroids synthesized and secreted by the ovary are estrogens, androgens, and progesterones. Estradiol (E_2), testosterone, and progesterone (P_4) are the most potent steroids in each of these respective categories. Dehydroepiandrosterone (DHEA), an androgen precursor hormone, is secreted by the adrenals.

Estrogen relieves the symptoms of the menopause[8, 15] and protects against osteoporosis,[6, 13, 35] and, although clinical trials have not been reported confirming this relationship,[7] observational studies suggest it offers significant protective effects from cardiovascular disease.[25, 48, 55] The risks associated with estrogen therapy include endometrial cancer,[16, 58] gallbladder disease,[56] and, possibly, an increase in breast cancer.[25] Progesterone downregulates estrogen receptors, protects against endometrial cancer in a dose and duration of therapy manner,[21, 57, 59] enhances protection from osteoporosis, and is a central nervous system sedative.[3] In addition, it has anti-aldosterone and anti-androgen properties. The androgens are important in maintaining skin, muscle, bone, and libido.[49, 50]

Clearly, there may be wide ranging consequences from deficiencies of these steroids. To use the term *deficient* suggests a definable level of

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these hormones that represents a normal range. Osteoporosis and cardiovascular disease are infrequent problems in premenopausal women. Because these serious and potentially lethal problems develop after the menopause when there has been a marked decline in these steroids, it seems reasonable to use premenopausal levels of these hormones as the normal range for replacement therapy. We have previously described the use of a continuous combined regimen of estradiol and progesterone which gave good relief of symptoms, uniformly produced an atrophic endometrium with a low incidence of bleeding, and caused no adverse effect on lipids.[28]

This manuscript presents a protocol for hormone replacement therapy in postmenopausal patients with measured deficiencies of E_2, testosterone, and DHEA. Formulating the appropriate replacement hormones requires individualizing therapy according to each woman's needs. Because progesterone is universally deficient in postmenopausal women, it is uniformly replaced unless precluded by side effects. Replacement dosage is accomplished by titrating the deficient steriod to levels present in premenopausal women. An appreciation of the mechanism of hormone action, the absorption kinetics of these hormones, and the first-pass effect on metabolism helps in trouble shooting problems encountered with therapy. To make valid comparisons over time, the serum hormones must be measured at a standardized time relative to the last dose. We believe this method of hormone replacement therapy is based on sound physiologic principles and represents an objective method of ensuring the establishment of premenopausal levels of circulating sex steriods. In short, it treats the menopause like a true deficiency state by correcting the measured hormone deficiencies.

MECHANISM OF HORMONE ACTION

Control of the female reproductive system during the premenopausal years is complex, involving a signal transduction cascade that begins in the cerebral cortex with neurotransmitter activation of the hypothalamus. In response to a variety of neurologic stimuli as well as sex steroid feedback, the hypothalamus signals pituitary secretion of gonadotropins through the release of GnRH. The gonadotropins, in turn, activate and control the development of the ovarian follicle and corpus luteum as well as the steroidogenic processes within these structures. The predictable and cyclic pattern of ovarian sex steriod production orchestrates and maintains a rather constant reproductive cycle for more than 35 years. Although the sex steroids are principally responsible for maintaining reproductive potential, these are extremely bioactive molecules which contribute to numerous end-organ responses in the normal, healthy adult. The strength of action of these molecules explains the degree of suffering which can accompany their loss following the menopause.

Ovarian Sex Steroid Production

All steroid hormones, including the sex steroids produced by the ovary, represent a subclass of lipids which share a four-ring structure called perhydrocyclopentanophenathrene. The native compound from which the sex steroids derive is cholestane, a C_{27} steroid, the parent of cholesterol. Under normal nutritional states, the principal precursor of steroidogenesis is plasma cholesterol, which enters cells through a lipoprotein receptor system. The ability of steroidogenic tissues to produce a particular class of steroids depends on the activity of enzymes within the cells of that tissue. During the reproductive years, the development and maturation of the ovarian follicle characterizes the first half of the menstrual cycle. As the follicle matures, the production of estradiol increases at a steady but gradual rate, and then rises at a near exponential rate before ovulation. A slight periovulatory rise in progesterone occurs while the postovulatory corpus luteum produces principally progesterone but also secretes significant amounts of estradiol. In addition to estradiol and progesterone, the ovarian stroma and thecal tissue of the follicle also produce a significant amount of androgen in response to gonadotropin stimulation.

Target Tissue Response to Sex Steroids

Although the measurement of circulating levels of steroids frequently is the standard by which the clinician determines endocrine status, the responsiveness of target tissues will ultimately determine the clinical effectiveness of any steroid level. As lipids, steroids can enter cells readily via passive diffusion. Tissues responsive to steroids possess specific intracellular receptors with a high affinity for their steroid ($K_d \approx 10\text{-}0.1$ nM). The binding of a steroid hormone to a receptor and subsequent interactions of this receptor-hormone complex with cellular components are considered to be the primary events in the mechanism of action of steriods. Within the cell, unoccupied steroid receptors reside in the nucleus, loosely associated with nuclear chromatin. Upon binding a steroid, the steroid-receptor complex becomes activated and binds with high affinity to specific regions within the promoter region of steroid-responsive genes.[58] Most effects of steroids on responsive cells are mediated through the activation of specific genes, which then leads to the production of specific cellular proteins. This genomic mechanism of action is relatively slow. Another more rapid membranous mechanism of action is now recognized. This is exemplified by the rapid effect of progesterone in causing capacitation of sperm.[26]

During the past several years, a great deal has been discovered relative to molecular mechanisms of signal transduction elicited by steroid hormones. Most of this information has come through a better understanding of steroid receptors. The sex steroid receptors have now been cloned,

and response elements have been identified in the promoter regions of steroid-sensitive genes.[61] Steroid receptors appear to demonstrate two zones of particular interest, a cysteine-rich region that appears to participate in DNA binding and a more highly conserved region that binds specific steroids. Estrogen and progesterone receptor concentrations are interrelated in a complex manner both physiologically and pharmacologically. The concentrations of both estrogen and progesterone receptors are controlled positively by estrogen and negatively by progesterone. Considerable but predictable changes in estrogen and progesterone receptors occur in both the brain and reproductive tract during the ovarian cycle. Similar, albeit less dramatic changes, may occur in other responsive tissues as well.

The Endometrium—A Classical Sex Hormone Responsive Tissue

Although menopausal changes in hormone status clearly affect the skeleton, the cardiovascular system, and the neurophysiological axis, the female genital tract and breasts are particularly responsive to changing levels of sex steroids. Within the genital tract the most steroid-sensitive tissue is the endometrium of the uterus.[16] The relatively high incidence of endometrial cancer in older women reflects the steroidal sensitivity of this tissue. A brief description of some recent studies in our laboratory may offer insight regarding the potential significance of sex steroid therapy. In the premenopausal endometrium, the concentrations of receptors for both estrogen and progesterone undergo characteristic variations throughout the menstrual cycle in response to the changing pattern of ovarian steroids. Estrogen receptor levels peak during the late proliferative phase, while progesterone receptors peak during the early luteal phase.[34] The concentrations of both estrogen and progesterone receptors are controlled negatively by progesterone, thus, receptors for each hormone decline by the end of the secretory phase. In contrast to what occurs in most adult tissues, extensive cell growth and tissue remodeling occur in a cyclic fashion within the uterine endometrium throughout a woman's reproductive life. During the estradiol-dominated proliferative phase, the endometrium repairs the wound left from the recent menstrual bleed and undergoes a time of rapid growth and remodeling. As progesterone becomes the dominant ovarian endocrine signal, growth of the endometrium is replaced by a period of cellular differentiation in preparation for pregnancy. In a nonfertile cycle, the blood levels of progesterone and estradiol decline rapidly, resulting in endometrial breakdown, bleeding, and tissue loss. The metalloproteinases (MMPs), a family of structurally related enzymes, are capable of degrading specific components of the extracellular matrix (ECM) and are thought to be physiologically relevant mediators of ECM composition and turnover during times of tissue repair and remodeling. The MMPs of the stromelysin family have been implicated in cancer invasion in the endometrium and breast.[39] Our laboratory has identified

specific mRNAs for the stromelysin family in the cycling endometrium and implicated these enzymes in mediating remodeling and breakdown of the endometrial ECM. The stromelysins were focally expressed in vivo in areas of tissue undergoing proliferation-associated remodeling and were broadly expressed during menstruation-associated endometrial breakdown; none of the stromelysins were expressed during the progesterone-dominated secretory phase of the cycle.[45]

We conducted in vitro studies which confirmed progesterone suppression of endometrial MMPs, but a stromal-derived factor was found to be necessary for progesterone-associated suppression of an epithelial-specific member of the stromelysin family, matrilysin. Additionally, we found no direct effect of estradiol on the induction of endometrial stromelysin expression. Because epidermal growth factor (EGF) and transforming growth factor-β (TGF-β) represent growth factors which can stimulate growth (EGF) or inhibit growth (TGF-β), we examined the possible role of these growth factors on endometrial stromelysin production. EGF was found to stimulate the endometrial stomelysins, while TGF-β was found to inhibit these enzymes.[46] Figure 1 summarizes the temporal relationships of endometrial MMP expression relative to the sex steroids, their receptors, and the growth factors which may regulate local tissue responses. Multiple studies have identified a myriad of cell- and tissue-specific growth factor that may direct steroidal action.[23] Clearly, in developing stragies for hormone replacement therapy, an awareness of these multiple interrelationships as a component of the predictive clinical benefit is critical.

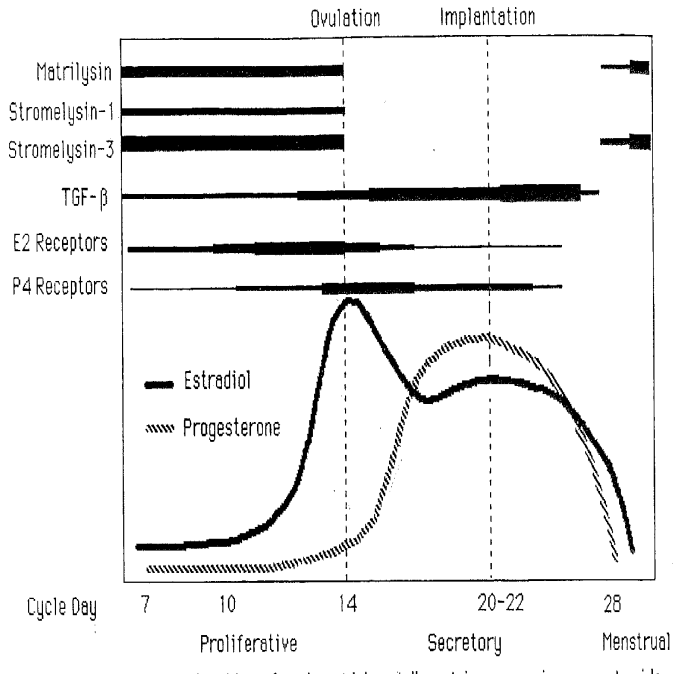

Figure 1. Temporal relationships of endometrial metalloprotein expression, sex steroids, receptors, and growth factors.

CHOICE OF SEX STEROIDS FOR HORMONE REPLACEMENT THERAPY

Several synthetic estrogens and progestins have been used for postmenopausal replacement hormonal therapy, both cyclically and as a daily combination. Potential disadvantages of these synthetic derivatives, in comparison with natural estradiol and progesterone, have been emphasized.[19, 20, 24, 30, 33, 38, 47] Preparations containing estrogens that do not occur naturally in women (conjugated equine estrogens, ethinyl estradiol, and diethylstilbestrol) have an exaggerated potency in the hepatic system relative to their estrogenicity.[24, 38] Preparations of synthetic progestins have variable dose- and formulation-dependent effects on lipoproteins. In particular, the 19-nortestosterone derivatives (norgestrel, norethindrone, norethindrone acetate, and norethisterone) increase LDL cholesterol and decrease HDL cholesterol concentrations, potentially reducing the beneficial cardiovascular effects of estrogen on these lipoproteins.[19, 20, 47] Synthetic progestins also decrease sex hormone binding globulin, resulting in an increase in free sex hormone levels and potentially increased androgenicity. The acetoprogesterone derivatives (medroxyprogesterone acetate) also exert a detrimental but less significant effect on lipoproteins.[30, 33]

When exogenous steroids are administered, they are eventually enzymatically degraded and eliminated. Metabolites are produced as a product of this enzymatic degradation process, and some are metabolically active. Furthermore, they may have metabolic consequences that are totally independent of the parent steroid and that frequently are poorly understood. For example, estradiol may, by way of the catecholestrogen pathway, act a surrogate catecholamine.[37, 53] The 5α-metabolites of progesterone may produce a sedative effect on the central nervous system by binding to the GABA receptors and opening the chloride channels. Testosterone may be aromatized to estradiol and have an estrogenic effect or be acted upon by 5α-reductase, become dihydrotestosterone, and have potent androgen effects. Therefore, the net effect of the administration of a single hormone is the sum of the metabolic effect of that hormone and the cascade of its metabolites. Additionally, the metabolic footprint of a particular steroid may vary in different individuals. We have reported this difference with the metabolites of progesterone.[3] Theoretically, this complicated effect could be greatly amplified by administering several estrogens simultaneously, such as conjugated equine estrogens. The number of potential metabolites and their metabolic consequences are appreciable.[9, 10]

Estradiol (17 beta-estradiol) and progesterone (4-pregnene-3,20-dione), as they occur naturally in humans, would appear preferential to their synthetic counterparts for estrogen replacement therapy. The bioavailability of estradiol following oral administration has been amply demonstrated.[43] We and others[12, 27, 40, 52] have demonstrated that a micronized natural progesterone preparation administered orally can produce excellent blood levels without unwanted side effects such as fluid retention, breast tenderness, weight gain, and depression, commonly associated with the synthetics progestins. Jensen and associates[31] demonstrated that

oral progesterone (200 mg) had no adverse effect on the beneficial changes in serum lipoproteins induced by the administration of estrogens. Our study confirmed this finding.[28] The metabolites of estradiol and progesterone frequently have important metabolic consequences. The metabolic footprint of foreign steroids in the human may be different from that of native sex steroids and may cause a variety of side effects. Estradiol and progesterone evolved with the human; therefore, these steroids would seem preferable for long-term replacement therapy.

If the deficiencies in the sex steroids are to be faithfully replaced, the androgens must be considered and, if deficient, included in the replacement program. The androgens are metabolically active in skin, muscle, and bone and are thought to have an important role in maintaining libido.[49, 50] In the skin, they support collagen and maintain oiliness by stimulating the pilosebaceous units. Androgens help maintain muscle mass and strength. Estrogens and androgens are necessary to maintain the optimum integrity of the musculoskeletal system. In keeping with our thesis that the best replacement hormones are those that occur naturally in the human, we prefer to use micronized testosterone with or without DHEA. When given at physiologic replacement levels, we have not observed an adverse effect on lipids. In contrast, methyltestosterone is commonly used as part of some hormone replacement programs. It has a dose-related deleterious effect on HDL cholesterol and, on rare occasions, may be hepatotoxic.[29]

HORMONE REPLACEMENT THERAPY WITH NATURAL SEX STEROIDS

Hormone replacement therapy should be individualized. The endpoint is satisfactory relief of menopausal symptoms and the demonstration of normal serum levels of estradiol.

Continuous Combined E_2 and P_4 for Safety and Compliance

Compliance with taking hormones is not a problem in the perimenopausal and early menopausal woman who is very symptomatic. As symptoms subside, continued menstruation is unacceptable to most women. With estrogen plus cyclic progestin regimens, regular uterine bleeding is expected and causes a significant problem with compliance. Continuous estrogen and progestin regimens were introduced in an attempt to improve compliance.[54] Although most women eventually become amenorrheic, breakthrough bleeding is an annoying and worrisome problem and causes many women to discontinue therapy.[4] Another potentially serious problem occurs when the progestin is selectively discontinued but the estrogen continued in a woman with an intact uterus. This sometimes occurs even though the importance of both hormones has been empha-

sized. The occurence of breakthrough bleeding when estradiol and progesterone are used in a continuous regimen is sufficiently uncommon that it does not cause compliance problems. Whenever possible, we combine the steroids to be used for replacement into a single capsule; selective omission is not possible with this method of therapy.

Replacement Levels of Estradiol

The menopause is characterized by a serum estradiol level that is less than 50 pg/mL. Such levels are insufficient to cause proliferation of the endometrium and allow withdrawal bleeding when challenged with progesterone. De Lignieres[18] found that postmenopausal women felt best and had fewer psychologic symptoms when serum levels of estradiol were titrated between 50 and 150 pg/mL. Interestingly, these levels approximate those seen during the course of a normal menstrual cycle. Levels less than 50 pg/mL were characterized by anxiety and depression, while levels greater than 150 pg/mL produced anxiety and irritability. Osteoporosis and cardiovascular disease are uncommon in menstruating premenopausal women. Therefore, the minimum measurable level of estradiol that is acceptable for replacement approximates 50 pg/mL. As the serum estradiol level exceeds 150 pg/mL, the symptoms and signs of hyperestrogenism progressively increase, that is, fluid retention, breast tenderness, food cravings, irritability, hot flashes, urinary frequency, and others reminiscent of the premenstrual syndrome. Because the normal menstrual cycle is characterized by estradiol levels ranging from 50 to 150 pg/mL of serum, we believe these values are reasonable as guidelines for determining replacement levels of estradiol.

Measurement of Serum Levels of Hormones to Ensure Adequate Replacement

Wide variation in the serum levels of estradiol among individuals is observed given the same dose of estrogen (Table 1). These levels vary from inadequate (<50 pg/mL) to excessive. Symptoms, such as vasomotor hot flashes, are not reliable indicators because they can be present with both high and low levels of estradiol. There is not a village or hamlet

Table 1. RANGE IN SERUM LEVELS OF ESTRADIOL 12 ± 2 HOURS AFTER ORAL DOSE OF CONJUGATED ESTROGENS AND MICRONIZED ESTRADIOL

Dose	Maximum (pg/mL)	Minimum (pg/mL)	Range (pg/mL)
Conjugated estrogens			
0.625 mg (n = 5)	268	88	180
1.25 mg (n = 4)	452	220	232
Micronized estradiol			
0.5 mg (n = 48)	380	5	375

now which does not have access to a clinical laboratory where serum estradiol levels can be obtained. The use of FSH and estradiol levels to diagnose the menopause but attempting to establish reasonable hormone replacement based solely on management of symptoms defies logic. To ensure adequate hormone replacement, timed serum levels of estradiol must be obtained and monitored.

Standardization of the Timing of Blood Samples for Hormone Measurement

Random determination of hormone levels may be misleading and generally not helpful in making clinical decisions concerning dosing during hormone replacement therapy. Absorption kinetics should be considered when serum hormone levels are being sampled. For example, when estradiol is given as a single dose, serum E_2 levels will be higher during the first 12 hours and lowest during the last 12 hours. Blood drawn at 12 hours yields an average estradiol level for that 24-hour interval between doses.[36] In the woman wearing a transdermal estradiol patch, the dosing is every 3.5 days (84 hours). To obtain an average level, the blood should be sampled on the second day (42 hours). Maintaining consistency in the timing of these hormone samples allows valid comparisons between measurements. From a practical standpoint, the oral hormone dose after which serum levels are measured should be taken at bedtime on the day preceding the sampling so that phlebotomy is performed 12 hours later during waking hours.

Route of Administration

All steriod hormones taken orally are absorbed from the intestinal tract into the splanchnic circulation which empties into the liver. The liver is the site of metabolism for steroid hormones. Steroids taken orally are presented to the hepatocytes in higher concentrations in the splanchnic blood than when they arrive through the systemic circulation from the ovary. This increased hepatic steroid load may have beneficial and, in some cases, unwanted effects. This first-pass phenomenon is important in understanding some of the problems occasionally encountered with hormone replacement therapy.

In view of the association of estrogen with cardioprotection, one of the most heralded effects of oral estrogen is its ability to increase HDL cholesterol. Hepatic protein synthesis is increased, which may lead to increased sex hormone binding globulin and other proteins that nonspecifically bind estrogen, leaving less free hormone available for estrogen action. Clotting factors may be increased, but this is usually not a problem at the replacement doses used clinically. In patients with a history of thrombophlebitis, the transdermal or another nonoral route may be warranted to obviate the increase in clotting factors. The renin-angiotensin-

aldosterone system may be activated through this mechanism and cause a rise in blood pressure. Again, this may be remedied by giving the estrogen via an extrasplanchnic routine.

An increase in metabolites may be another effect of the high level of hepatic steroids. These metabolites can have annoying and unwanted side effects. For example, the increased formation of catecholestrogens could contribute to vasomotor symptoms some patients experience even though normal circulating levels of estrogen are present. Some of the metabolites of progesterone have sedative qualities and may cause drowsiness. This effect of progesterone can be advantageous in managing the insomnia frequently encountered at the menopause; however, excessive sedation that leaves a hangover is unacceptable. Changing the route of administration or dosage may relieve the symptoms by changing the rate of formation of these metabolites.

The oral route of administration increases the steroid load in the bile, and this may contribute to increased formation of gallstones. Each route of administration is associated with problems. For example, the trandermal estradiol patch may cause skin irritation and rashes which may preclude its use. For most patients, the oral route is well-tolerated, available, convenient, and more economical than other delivery systems. It is our choice to begin therapy with the understanding that it can be changed or modified.

EVALUATION PRIOR TO INSTITUTING HORMONE REPLACEMENT THERAPY

History and Physical Examination

The success of treatment depends on an accurate diagnosis. History and physical examination are basic to making most diagnoses in medicine, and evaluation for the menopause is no different. Menstrual history is clearly important. If the patient is still menstruating, estrogen deficiency is unlikely because it usually takes serum levels of greater than 50 pg/mL of estradiol to proliferate the endometrium sufficiently for bleeding to occur. A history of hysterectomy or removal of the ovaries should be noted.

Vasomotor symptoms, either in the form of hot flashes or sweats, occur in 85% to 90% of menopausal women; however, hot flashes are not synonymous with estrogen deficiency. Oldenhave[44] reported the occurrence of hot flashes in 41% of regularly cycling women more than 39 years of age. Hot flashes reached their maximum frequency of 85% at the menopause. Fifty-seven percent of the study patients were still having hot flashes more than 10 years after the menopause. Hot flashes have been documented in women with the premenstrual syndrome, a condition that has not been characterized by estrogen deficiency. It is unlikely the 41% of premenopausal patients experiencing hot flashes in Oldenhave's study were estrogen-deficient. We have repeatedly observed hot flashes in patients with normal or elevated serum E_2 levels. Some of these vasomotor symptoms can be mediated by estrogen metabolites such as catecholestrogens behaving as surrogate catecholamine. Hot flashes can occur at various circulating levels of estrogen and cannot be considered the sine quo non of estrogen deficiency. Other conditions associated with hot flashes are as follows:

Estrogen deficiency or excess
Endocrine disorders: hyperthyroidism, pheochromocytoma, carcinoid
Pregnancy and postpartum
Psychiatric disorders: panic attacks
Drug and endocrine therapy: nicotinic acid, sympathicomimetic drugs, GnRH analogues, clomiphene citrate, tamoxifen, birth control pills

An inability to concentrate, feelings of depression or anxiety, and insomnia are common complaints. The symptom of aching joints leads many of these women to think arthritis is developing. The review of systems should provide information on the use of alcohol, tobacco, and drugs, both prescription and nonprescription types. Family history of cardiovascular disease, malignancies, and osteoporosis should be noted.

Physical examination should include the taking and recording of height, weight, and blood pressure. Special attention should be directed to organs that are targets of estrogen therapy, such as the thyroid, breasts, and reproductive organs. Mammography, if not current, should be scheduled. A Papanicolaou smear should be obtained. Estrogen deficiency of some duration will be evident by atrophic changes of the breasts and reproductive tract. Short-term loss of estrogen may not be readily apparent.

Laboratory Studies

The finding of an FSH level greater than 50 mIU/mL and an E_2 level less than 50 pg/mL of serum provides laboratory confirmation of ovarian failure. In addition to laboratory findings of elevated gonadotropin and deficient estrogen, traditionally, 12 consecutive months of amenorrhea are required to confirm the diagnosis of menopause. Levels of the androgens, testosterone, and dehydroepiandrosterone sulfate (DHEAS) should be obtained to determine their role in the hormone replacement protocol. Because some of the symptoms seen with the menopause may also be present with thyroid disease, an estimate of thyroid function by measurement of TSH and T_4 levels may be helpful.

A complete blood count and urinalysis should be part of the general evaluation. Measurement of blood sugar and lipids or one of the automated chemistries providing these data should be performed for baseline information.

Imaging and Biopsy

We do not routinely perform imaging studies before instituting hormone replacement therapy. Patients with a history of abnormal bleeding

should undergo vaginal sonography and, in most cases, endometrial biopsy. Pipelle (Unimar, Wilton, CT) endometrial suction curettage is an accurate procedure that can usually be accomplished in the office with little or no anesthesia. If the endometrial stripe can be clearly identified with vaginal sonography, is not obscured by leiomyoma or polyps, and its double-wall thickness is no more than 5 mm biopsy is not done.[7] In women who do not fit these criteria or in those with persistent bleeding, endometrial sampling should be accomplished and histology scrutinized. In asymptomatic patients taking unopposed estrogens, annual sonography and endometrial biopsy are necessary for the detection of developing hyperplasia. Any bleeding in these patients should be considered abnormal, and they should be promptly evaluated by sonography and biopsy.

In women with a strong family history of osteoporosis, baseline bone mineral content studies are useful in assessing risk. This information may be helpful to convince patients who are reluctant to enter into long-term hormone replacement programs unless there is objective demonstrated medical necessity.

Candidates for Hormone Replacement Therapy

Women who are surgically castrated or who have laboratory demonstrated E_2 levels less than 50 pg/mL and FSH levels greater than 50 mIU/mL in serum are candidates for hormone replacement therapy. In the past, endometrial and breast cancer have been considered contraindications to estrogen therapy; however, this opinion has recently been questioned.[14, 17] All patients should be enlightened as to the risks and benefits of estrogen replacement therapy. This discussion should be clearly documented in the patient's medical record. The decision to start hormone replacement therapy should be made jointly between an informed patient and her physician. This becomes especially important if the decision to institute therapy is controversial, such as in women with a history of breast or endometrial cancer.

Encouraging a Healthy Lifestyle

Women face many and varied stresses at this time in life other than the physiologic and endocrinologic changes associated with the menopause. Children may be leaving home (the empty nest) or returning (the revolving door). Some are faced with the care of elderly parents (eldercare). Pressures from work and running a household are still the dual lot of a great many women. It should be no surprise that fatigue is one of the more common complaints voiced by these women.

A physically well-conditioned body withstands stress better. Regular aerobic exercise should be encouraged. The equivalent of 30 minutes of brisk walking at least 5 days per week is strongly recommended. The

exercise should be sufficiently vigorous to raise the pulse, usually to 110 to 120 bpm or around 70% of maximum. This may be calculated by the following formula: 220 minus age times 70% equals target pulse rate. This should be used as a guideline. The individual who is in miserable physical condition and beginning an exercise program will need to start at a slower pace and gradually increase the exercise as conditioning occurs.

Patients should be instructed to eat a low-fat diet such as that recommended by the American Heart Association. Cultures who consume diets low in fact, such as the Japanese or rural Chinese, have less symptoms with the menopause. Some of this effect is thought to be from their high consumption of phytoestrogens, which are estimated to be around 50 times more than in the typical Western diet.[2] Phytoestrogens are particularly abundant in soya products.[5, 11, 41] Some vitamin supplements are frequently helpful. Many women in the perimenopausal transition experience premenstrual symptoms, including fluid retention, irritability, moodiness, and breast tenderness. Vitamin B_6, 200 mg, and vitamin E, 400 U daily, are frequently helpful.[1, 51]

INSTITUTING HORMONE REPLACEMENT THERAPY

Diagnosis

Ovarian failure is diagnosed in an irregularly menstruating or amenorrheic woman who has an FSH level greater than 50 mIU/mL and an estradiol level less than 50 pg/mL in serum. Although the amenorrhea must be present for 1 year to establish firmly the diagnosis of menopause, hormone replacement therapy should be considered when the diagnosis of ovarian failure is established. Because estradiol levels of approximately 50 pg/mL in serum are required for withdrawal bleeding to progesterone, it is very unusual to find an estrogen deficiency of less than 50 pg/mL in regularly menstruating women.

The Regularly Menstruating, Euestrogenic, Eugonadotropic but Symptomatic Perimenopausal Woman

Serum E_2 and FSH levels should be measured at a time other than menstruation to clarify the endocrine status. Measuring E_2 and FSH during menstruation can be confusing, because the new cohort of follicles are being recruited for the upcoming cycle, therefore, E_2 is low and FSH is elevated. Because approximately 50 pg/mL of E_2 is necessary for menstruation, these women are likely to have an E_2 level above 50 pg/mL, and hot flashes are best treated by progesterone alone. This can be accomplished with micronized progesterone, 100 mg orally three times daily, given the sixteenth through the twenty-seventh days of each cycle. If excessive drowsiness is encountered from the oral progesterone, it may

be given as a vaginal suppository, 25 to 50 mg during the same days. Alternatively, norethindrone acetate, 5 mg, or medroxyprogesterone acetate, 10 mg, may be given the sixteenth through the twenty-fifth days of each cycle. If withdrawal bleeding fails to occur, the progesterone or progestin is continued on a monthly basis with the dosage given on the same days as taken in the preceding month. Failure to have bleeding for 3 consecutive months in the face of this cyclic progesterone usually indicates the estradiol level has dropped below 50 pg/mL. This should be confirmed by assaying the serum E_2 and adding estrogen to the hormone replacement program.

In some patients with intermittent symptoms due to wide fluctuations in estradiol levels, a small daily dose of E_2, 0.25 mg, with P_4, 50 mg, is added to the cyclic progesterone or progestin. When endogenous estradiol production ceases, these women become amenorrheic even in the presence of cyclic progesterone. At that time, they can have serum levels of E_2 titrated to appropriate levels.

The Hypoestrogenic Hypergonadotropic Woman

In the hypoestrogenic, hypergonadotropic woman, ovarian failure has occurred. Because the oocytes are depleted, no follicle or corpus luteum will be formed. Estradiol deficiency is confirmed by obtaining a serum of E_2. Because progesterone is essentially a corpus luteum product, measuring it is superfluous and increases laboratory costs. To institute faithful hormone replacement requires the use of two steroids, E_2 and P_4. For convenience and to enhance compliance, therapy is started by giving a single capsule containing 0.5 mg of E_2 and 100 mg of P_4 daily at bedtime. An example of blood levels obtained in patients taking this mixture is presented in Table 2.

After the patient has been undergoing this therapy for 1 month and has come into a steady state with the hormones, the serum estradiol level is checked 12 hours after the last dose of the E_2 and P_4 capsule. The targeted range is 50 to 150 pg/mL for serum E_2, and the dose should be titrated on an individual basis to arrive at this range. E_2 doses will range from 0.25 to 2 mg orally and from 0.05 to 0.1 mg transdermally, depending on the individual.

Experience has taught us that P_4 levels do not need to be measured routinely when giving this steroid on a continuous basis. We[28] and others[22]

Table 2. BLOOD LEVELS ON CONTINUOUS ESTRADIOL AND PROGESTERONE THERAPY (n = 52)

	Control ± SEM	Treatment ± SEM	*P* Value
Estradiol	20 ± 3 pg/mL	126 ± 9 pg/mL	< 0.0001
Progesterone	0.3 ± 0.1 ng/mL	2 ± 0.2 ng/mL	< 0.0001

Serum levels of estradiol and progesterone were measured at control and 18 hours after receiving a single daily capsule containing estradiol, 0.5 mg, and progesterone, 100 mg (E_2P_4), one daily for 3 weeks.

have found that low doses of daily, continuous oral P_4 uniformly prevent hyperplasia and cancer. Of course, when the hormones are given cyclically, proliferation of the endometrium occurs. In this setting, substantially more progesterone (300 mg of micronized P_4) is required to effect secretory transformation and allow orderly withdrawal bleeding.[32,60] Figure 2 illustrates the atrophic changes found in the endometrium in the woman taking continuous daily E_2, 0.5 mg, and P_4, 100 mg, for 15 months.

Some women will continue to have hot flashes and sweats despite the demonstration of normal circulating levels of E_2. Characteristically, these hot flashes are worse during the first 3 to 4 hours following the ingestion of the E_2, a time when E_2 absorption kinetics should place the E_2 at peak levels. Oral ingestion of E_2 involves the first-pass phenomenon, and this enhances the formation of E_2 metabolites in the liver. We have postulated that catecholestrogens so formed may be responsible for the vasomotor symptoms by acting as surrogate catecholamines or as antiestrogens. Amelioration of the symptoms can usually be effected by changing the route of administration of E_2 to a nonoral route, which avoids the first-pass effect by the liver. The transdermal E_2 patch can be used with the dose sufficient to maintain an E_2 level greater than 50 pg/mL. Other preparations which avoid absorption into the splanchnic circulation include vaginal E_2 tablets, capsules, creams, and rings; transdermal E_2 gels; subcutaneous E_2 pellets; and parenteral E_2 injections. Correction of the menopausal symptoms by changing to an extrasplanchnic route of administration is supportive evidence for the metabolites being responsible for vasomotor symptoms.

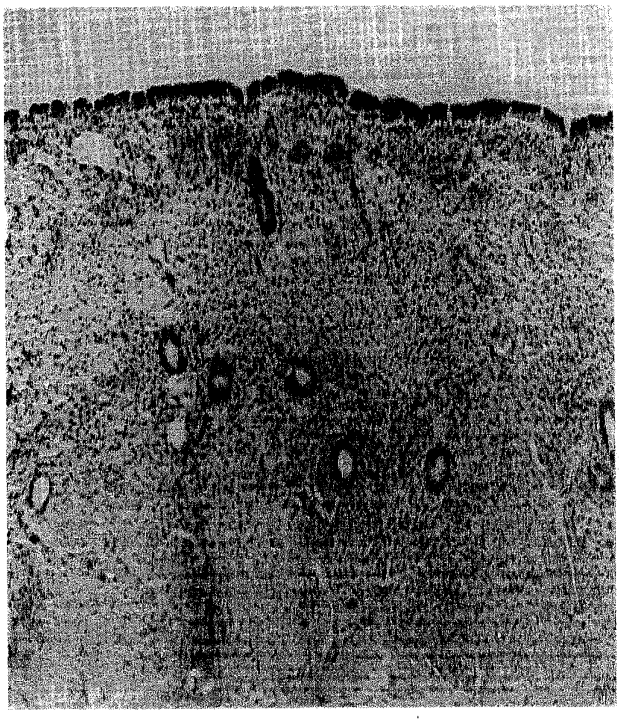

Figure 2. Endometrium showing atrophy, from hysterectomy specimen 15 months on continuous estradiol and progesterone.

When androgens are confirmed to be deficient by measurement, we add either micronized testosterone, 5 mg, (Table 3) or micronized DHEA, 25 mg, to the E_2 and P_4 capsule. Because DHEA is a precursor hormone for testosterone biosynthesis, the addition of testosterone is unnecessary when DHEA is chosen for replacement therapy. We consider the normal range of testosterone to be from 0.2 to 0.6 ng/mL. Excess androgen symptoms, such as oily skin, acne, and hirsutism, are not usually encountered if these levels are not exceeded. DHEAS measurements are generally available from most laboratories. DHEAS is the principle metabolite of DHEA, and its level correlates well with the parent compound.[42] DHEAS levels of 800 to 3300 ng/mL are considered normal in our practice.

FOLLOW-UP ON HORMONE REPLACEMENT THERAPY

Follow-up visits are scheduled at monthly intervals until there is satisfactory control of symptoms. As previously indicated, this requires administering the proper dose of E_2 that supplies normal premenopausal levels of this steroid. Persistent symptoms may require a change in the route of administration of the E_2 from an oral to transdermal or other extrasplanchnic route. Unless there is a specific intolerance to progesterone, it is given as a part of the hormone replacement regimen in all women, history of hysterectomy notwithstanding. After these criteria are met, annual follow-up is advised. The hormone replacement is continued indefinitely.

TROUBLE SHOOTING PROBLEMS ASSOCIATED WITH HORMONE REPLACEMENT THERAPY

Bleeding

When patients meet the criteria for menopause, that is, 1 year of amenorrhea, an E_2 level of less than 50 pg/mL, and an FSH level of greater than 50 mIU/mL, uterine bleeding is uncommon and should be

Table 3. BLOOD LEVELS ON CONTINUOUS ESTRADIOL, PROGESTERONE, AND TESTOSTERONE THERAPY (n = 56)

	Control ± SEM	Treatment ± SEM	*P* Value
Estradiol	23 ± 2 pg/mL	116 ± 9 pg/mL	<0.0001
Progesterone	0.3 ± 0.04 ng/mL	2.2 ± 0.2 ng/mL	<0.0001
Testosterone	0.2 ± 0.02 ng/mL	0.3 ± 0.05 ng/mL	<0.2959 (NS)

Serum levels of estradiol, progesterone, and testosterone were measured at control and 18 hours after receiving a single daily capsule containing estradiol, 0.5 mg, progesterone, 100 mg, and testosterone, 5 mg (E_2P_4T), one daily for 3 weeks.

investigated initially by vaginal sonography. When the endometrial stripe can be well-identified and measures less than 5 mm in double-wall thickness (Fig. 3), a malignant cause for the bleeding is highly unlikely. If the stripe measures more than 5 mm, is not clearly identified (Fig. 4), or the bleeding is persistent, biopsy of the endometrium is indicated to establish the diagnosis. The true nature of a thickened endometrium may be clarified by a sonohysterogram, that is, the instillation of intrauterine saline during sonography (Fig. 5). The Pipelle biopsy correlates well with tissue diagnoses from dilation and curettage. It is convenient, can usually be accomplished as an office procedure, and is less expensive than other procedures done in same day surgery or other hospital settings. Hysteroscopy and directed biopsy are indicated if the bleeding is persistent and remains unexplained.

Hyperestrogenism

Irritability, fluid retention, mood swings, food cravings, hot flashes, fatigue, breast pain, and other symptoms reminiscent of the premenstrual syndrome in a patient receiving hormone replacement therapy are most commonly encountered with too much estrogen, either from an elevated serum level of E_2 or upregulation of estrogen receptors. An appropriately timed serum estradiol level should be obtained. Progesterone in oil,

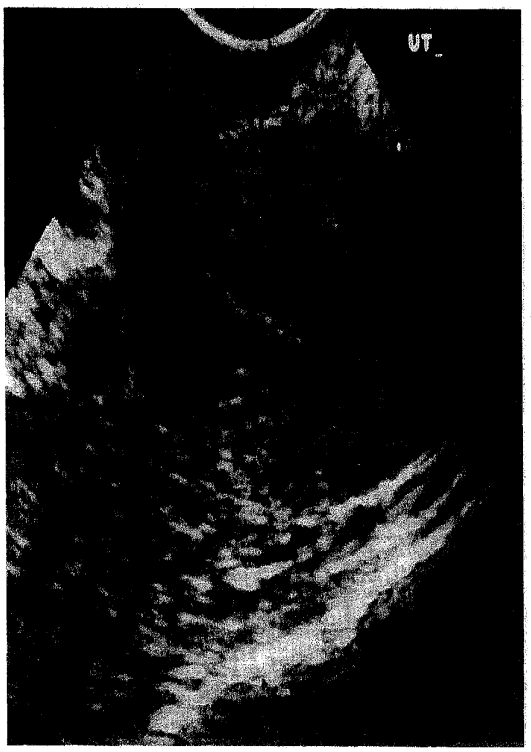

Figure 3. Postmenopausal bleeding from an atrophic endometrium. Patient taking continuous estradiol and progesterone as hormone replacement therapy. (Courtesy of Arthur C. Fleischer, MD and Donna M. Kepple, RT, RDMS, Nashville, TN)

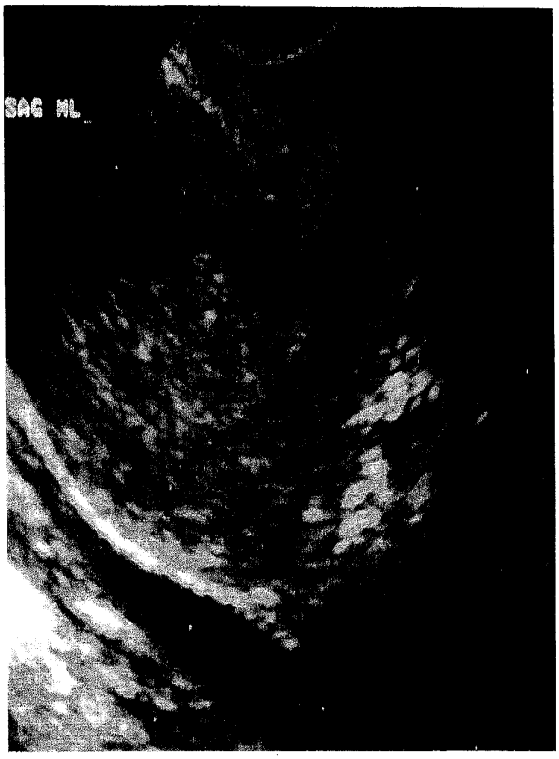

Figure 4. Postmenopausal bleeding from adenocarcinoma. Patient using transdermal estrogen patch, unopposed for 2 years. (Courtesy of Arthur C. Fleischer, MD and Donna M. Kepple, RT, RDMS, Nashville, TN)

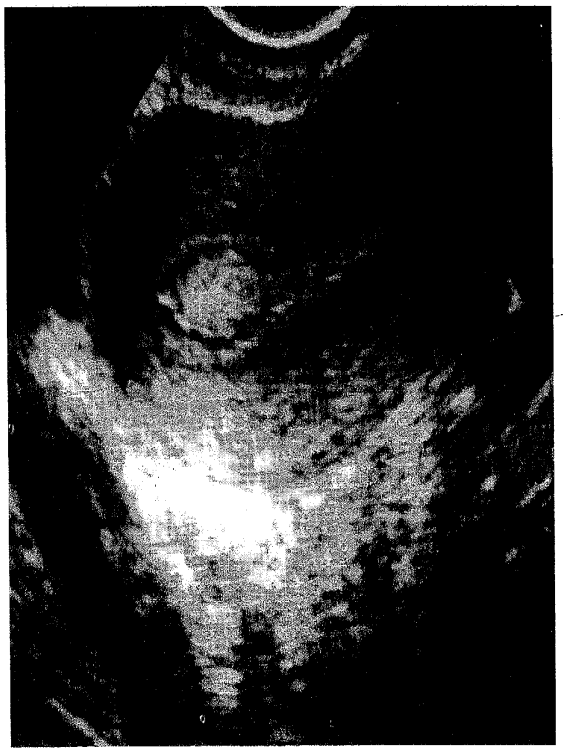

Figure 5. Sonohysterogram demonstrating an endometrial polyp as the cause for postmenopausal bleeding in a patient receiving continuous estradiol and progesterone for hormone replacement therapy (Courtesy of Arthur C. Fleischer, MD and Donna M. Kepple, RT, RDMS, Nashville, TN)

100 mg given intramuscularly, usually relieves these symptoms within a matter of hours. Alternatively, the hormone therapy can be omitted for 3 to 5 days while awaiting laboratory results. Most patients will feel better when they return; especially, if they have received progesterone. For those who experience no relief of symptoms, the E_2 level is now available to guide changes in therapy.

Progesterone Problems

Problems with natural progesterone are infrequent and relate to sedation. Most of these can be managed successfully by reducing the dose or changing the route of administration.

CONCLUSION

Using the sex steroids which occur naturally in humans represents faithful replacement of the steroids lost at ovarian failure. By using timed measurements of the replaced steroids to ensure attainment of premenopausal levels of the deficient hormones, the woman can be assured of the adequacy of therapy—not too little and not too much. This method of hormone replacement has been evolving for more than 10 years. Approximately 6 million doses have been given to a large number of women during this period of time. This is an inexpensive therapy that gives good relief of symptoms and is well-tolerated. The endometrium is protected, and uterine bleeding is infrequent. Patient compliance is good, and the positive effects of this hormone treatment encourage most patients to want long-term therapy.

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PREVENTIVE HEALTH CARE FOR THE MENOPAUSAL WOMAN

Susan L. Warner, MD, MPH

Women currently live about one-third of their lives after the menopause and will have a projected life expectancy of 81 years by the middle of the next century according to the 1977 US census. Premature deaths and illnesses caused by infectious diseases, which characterized the first era of modern medicine, have largely been replaced by cardiovascular diseases and cancer as the major causes of mortality. The future scope of medicine will focus more on the quality of life in the later years, specifically as it relates to loss of vision and hearing, impaired memory and cognitive function, decreased independence, and diminished strength and reserve.[27] Although interventions to prevent disease from occurring will remain a high priority, prevention of further morbidity from established diseases by screening, patient education, and expectant monitoring of health status will increasingly occupy the attention of physicians.

The emergence of health care policy and the changing economics of medical practice have challenged physicians to consider not only quality and efficiency but also cost and effectiveness in the delivery of care. In light of these concerns, practitioners of preventive health care must evaluate the scientific basis of any widely recommended practice and develop systematic methods to ensure adherence to guidelines. A growing body of literature has focused attention on the lack of effectiveness of the routine physicial examination and the need to identify patients at risk for disease so that selective education and screening can occur.

Furthermore, effective management of the office environment with tools such as preventive care flow sheets, reminder systems, and health

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