Estrogen and Progesterone: A Review

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Abstract

A review of the major sex hormones (progesterone, the estrogens and testosterone) is presented with a clinical focus on hormonal implications of osteoporosis, heart disease and menopausal symptoms. Within this summary overview, an initial discussion of "natural" versus "synthetic" hormones is presented.

RESEARCH REVIEW

Introduction

Men and women both synthesize three major gonadal hormones: estrogen, progesterone, and testosterone. The differing balances of these three hormones in men's and women's bodies affect the development of the reproductive organs as well as many other body systems and organs.

The human body synthesizes hormones from cholesterol (see Figure 1). These organic molecules are produced and secreted by one organ and then carried via the blood stream to another organ where they cause a specific response in the target tissue. Three major factors determine the effect of the hormone: first, the molecule must bond to the appropriate cell receptor site; second, the molecule must deliver a specific "message" to the cell, which is determined by the molecular structure of the hormone; and third, the receiving cell must be able to respond to the hormonal "message." The same hormone will evoke different biological responses in different types of cell tissue. Hormones are extremely potent messengers within the body, and even slight variations in molecular structure will alter the effect of the hormone on the target cell.

During childhood and after menopause, estrogen and progesterone remain at relatively constant levels in a woman's body. During the reproductive years, estrogen and progesterone follow a rhythmic cyclical pattern of approximately 20-40 days, with an average of 28 days per cycle (see Figure 2). During the proliferative phase (from the end of menses to ovulation), the ovaries secrete estrogen in response to hormones secreted by the anterior pituitary — Follicle Stimulating Hormone (FSH) and Leutenizing Hormone (LH). Ovulation is linked with a sharp rise and fall in estrogen at midcycle. After ovulation, the follicular cells in the corpus luteum transform into luteal cells, which respond to the stimulation of LH (and, to a lesser degree, FSH) by producing progesterone. The post-ovulatory secretory phase is marked by an increase in progesterone and a decline in estrogen production. Both estrogen and progesterone drop markedly before the onset of menses.

Progesterone

Produced in the luteal cells of the corpus luteum and in the adrenal cortex, progesterone is synthesized from cholesterol. In the ovary, LH stimulates the production of progesterone, following ovulation. In the adrenal cortex, progesterone is the precursor of adrenal steroids, including corticosteroids, as well as testosterone, estrone, and estradiol. In contrast, synthetic progestins, discussed in more detail below, are

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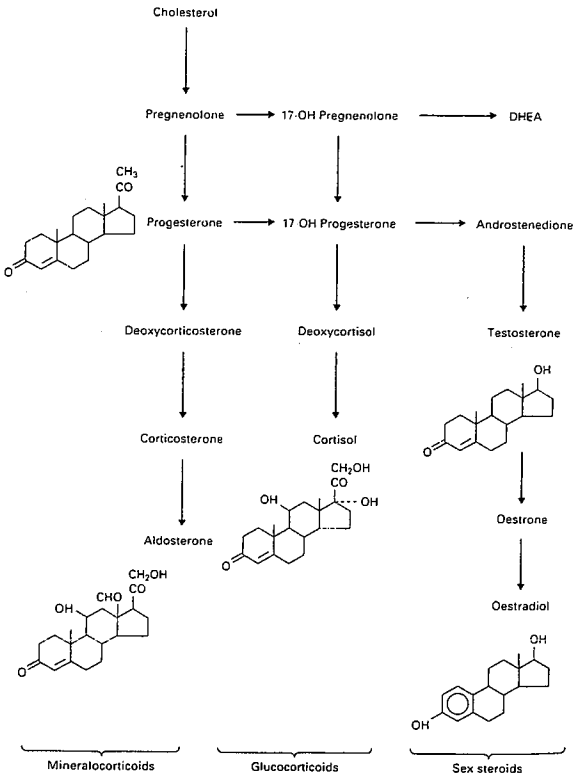

FIGURE 1

metabolic end-points (i.e., they do not function as precursors for other hormones.)

Progesterone's structure is very similar to testosterone, differing only in the fragment attached to the carbon-17 position. This structural resemblance may account for the greater similarity of the effects of progesterone and testosterone in the body as compared with the effects of estrogen. Progesterone's sphere of action includes salt regulation, lysosome stabilization, blood sugar control, stabilization of nerve functions, and promotion of a healthy thymus gland. (1)

INTERACTION WITH OTHER HORMONES

During a "normal" response to stress, a healthy adrenal gland increases cortisol production and thus decreases progesterone levels as progesterone is shunted into the adrenal steroid pathway. As progesterone levels drop, estrogen relatively increases in the bloodstream. This increase in estrogen levels causes many symptoms associated with PMS including breast tenderness, water retention, and irritability. During high-stress periods when the body is producing more cortisol, a woman may be more inclined to experience Premenstrual Syndrome (PMS), a condition exacerbated by a predominance of estrogen in the luteal phase.

A prolonged period of stress may lead to "adrenal exhaustion," with an accompanying decrease in cortisol production. One of cortisol's functions is pain relief; hence, a woman with adrenal exhaustion may experience dysmenorrhea as a result of reduced cortisol output. R.F. Peat, PhD suggests that progesterone supplementation would provide the precusor for the adrenal steroid pathway, thereby increasing cortisol production and reducing menstrual cramping. (1a)

Synthetic progesterones, also known as "progestins" or "progestogens," mimic but do not duplicate the effects of natural progesterone. Clinical studies demonstrate that women suffering from PMS improve with natural progesterone therapy, while progestin supplementation exacerbates the condition. (2) For the purposes of this article, "natural progesterone" refers to products derived from Mexican wild yam or soybean plants. Supplementing progestins, e.g. for birth control or hormone replacement therapy (HRT), actually drives down the levels of natural progesterone, and again causes a relative excess of estrogen in the blood stream. This relative increase in estrogen accounts for many of the side-effects associated with HRT. Additionally, as discussed in more detail below, the altered progesterone molecule delivers an altered "message" to the target cells in the body, generating a host of additional side-effects.

Other actions of progesterone include reducing the breast cell proliferative activity of estrogen (3), and decreasing breast cancer rates in women receiving estrogen therapy. (4) Synthetic progestins, however, do not offer protection against breast cancer when combined with estrogen therapy. The authors of one study conclude that the substantially increased risk of breast cancer among older women on HRT should be carefully assessed. (5) Another study of 1,083 infertile

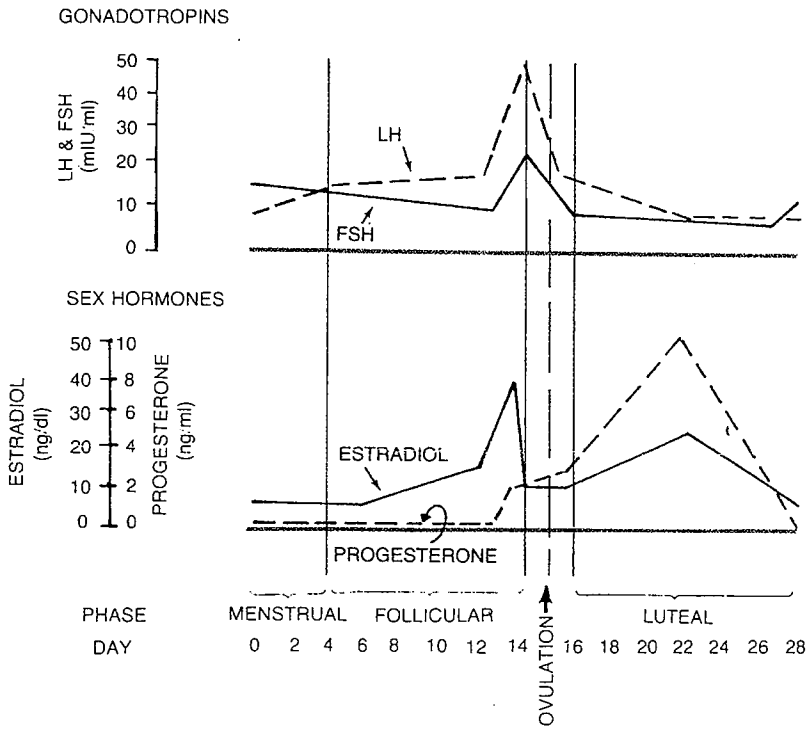

FIGURE 2

women followed over 14-34 years linked decreased progesterone levels with a five-fold increase in premenopausal breast cancer. (6) Clearly, the conventional wisdom of prescribing unopposed estrogen for women following hysterectomies is flawed if the women still has her breasts. Natural progesterone, as opposed to progestogens, would be the therapy of choice to reduce breast cancer risk for women taking HRT.

Some physicians reluctantly add progestogens to the HRT prescribed for postmenopausal women because synthetic progesterone lowers HDL cholesterol levels. One of the presumed benefits of estrogen therapy is an increase in HDL levels (with an accompanying overall increase in cholesterol levels). Research conducted on postmenopausal women taking progestin versus natural progesterone therapy demonstrated that progestins significantly lowered HDL cholesterol while natural progesterone had *no effect* on HDL levels. (7)

Because most of the studies on preventing osteoporosis have focused on estrogen, many researchers have overlooked the effects of progesterone on bone mineral density. (8) Estrogen supplementation alone *arrests* bone mineral loss in postmenopausal women, while natural progesterone therapy actually *increases* bone mineral density independent of estrogen supplementation. One study followed 100 postmenopausal patients, aged 38-65, over a three year period. The women followed a program of natural progesterone cream application, dietary changes and restrictions, vitamin supplementation, exercise, and estrogen replacement therapy unless contraindicated. All women showed an increase in bone mineral density, with the greatest increase occuring during the first year. On average, bone mineral density increased 10% in the first 6-12 months, followed by an annual increase of 3-5% until bone mineralization levels stabilized at the level of healthy 35-year-olds. Neither age nor time from menopause affected the bone remineralization rates. The study demonstrated no significant difference between those women receiving progesterone supplementation alone and those receiving concomitant estrogen therapy. (8)

While progestins adversely affect a developing fetus, natural progesterone may be beneficial during pregnancy. Neil H. Laurersen MD, in his book *Premenstrual Syndrome & You*, cites a study conducted by Katharina Dalton, MD of 90 children whose mothers received prenatal progesterone compared to a control group. At six months, more of the progesterone-supplemented mothers were still breast-feeding; more of the children were standing and walking at one year; and at 9-10 years of age the children showed superior performance in several academic areas, including verbal reasoning, English, arithmetic, and craftwork. The progesterone-supplemented children's physical education performance matched those in the control group. None of the mothers receiving ante-natal progesterone experienced toxemia, while more than half of the control group experienced toxemia. (9)

Natural progesterone may be administered in two forms — micronized progesterone, which is administered orally, and progesterone in a cream base that may be applied to hairless skin and/or vaginal tissue. Researchers first isolated natural progesterone in 1934 but found that orally ingested progesterone broke down into an inactive form in the intestines. Eventually researchers experimented with pulverizing the progesterone into minute particles, a process called micronization. This preparation, however, could not sustain progesterone levels long enough to stimulate menstruation. Not until the 1980's did researchers develop a capsule of 200 mg of micronized progesterone suspended in oil that provided longer sustained levels of progesterone in the bloodstream. Manufactured under the name "Utrogestan," this micronized progesterone capsule is widely used for hormone replacement therapy (HRT) in Mexico and Europe. According to *Women's Health Watch*, Schering, a pharmaceutical company, " . . . plans to market (Utrogestan) as Prometrium in the U.S., but doctors won't be able to prescribe it for HRT until it is approved by the FDA for treatment of secondary amenorrhea, as many of the progestins were originally." (10)

Micronized progesterone is a 10% solution, while progesterone cream is a 3% solution. The micronized progesterone will relieve severe symptoms more quickly than topically applied progesterone cream.

Progesterone cream may be applied to non-hairy areas (e.g., the chest, breasts, lower abdomen, inner thighs, etc.). The application site should be rotated periodically. Sometimes the application site relates to a particular condition, e.g., applying progesterone cream to the lower abdomen to relieve menstrual cramping, or directly to the vaginal tissue for treatment of vaginal dryness. The rate of absorption seems to relate to the body's "need" for progesterone. (11) From the cessation of menses to the week before menses, the cream usually absorbs in two to three minutes, while the week before menses the cream generally absorbs in a minute or less.

The following dosages of progesterone cream are based on recommendations cited in *Natural Progesterone: The Multiple Roles of a Remarkable Hormone:* (12)

PMS: begin application the day after ovulation,
1/8 tsp BID day 15-18
1/4 tsp BID days 19-23
1/2 tsp BID until onset menses
Taper the dosage over time until the patient is symptom-free with no applications.

Dysmenorrhea: The cream can be used during menses to stop cramping. Apply to the lower abdomen.

Menopause, menstruating:
No cream application during menses.
1/4 tsp BID day 7-21
1/2 tsp BID day 21 to onset menses.

Menopause, no menses: use calendar month.
No cream days 1-7
1/4 tsp BID days 8-21
1/2 tsp BID days 22-31

Natural progesterone alone may relieve vasomotor flushes. Use progesterone cream every 15 minutes during a hot flash. If hot flashes continue after one month, consider adding estrogen to the natural progesterone therapy.

Osteoporosis prevention: begin with serial dual photon absorptiometry or dual energy x-ray absorptiometry to establish bone mineral density (BMD) baseline. Follow calendar month:

No cream days 1-7

1/4 tsp cream BID days 8-31

Osteoporosis, severe: Follow calendar month.

No cream days 1-7

1/4-1/2 tsp days 8-31

For severe cases of osteoporosis, consider using micronized oral progesterone in addition to topical cream application.

Women concurrently taking thyroid medication should be monitored carefully, as the increased progesterone levels may potentiate thyroid activity.

For menopausal women wanting to replace synthetic progestin therapy with natural progesterone supplementation, Bajamar Women's Health Care reports that women using five mgs. of synthetic progestin will need a corresponding dose of 50 to 500 mgs of micronized progesterone. "A dosage of 100 milligrams twice a day or 200 milligrams per day of natural progesterone will usually produce endometrial conversion or prevent hyperplasia (endometrial overgrowth)." (13)

SYNTHETIC PROGESTINS

As mentioned earlier, synthetic progesterones, most accurately called "progestins" or "progestogens", catalyze different actions in the cell tissues than natural progesterone. According to J.R. Lee, MD, "It is clear that, while the basic progesterone molecule is present, there exist several alterations, e.g., acetate or ethinyl groups linked the carbon-17 site. The implication is that, with the A ring unchanged, these compounds may occupy the same receptor sites as natural progesterone, but the 'message' is different. This undoubtedly explains the alarming array of their *PDR* listed warnings . . . ." (14) The listed warnings include edema, cholestatic jaundice, nausea, fatigue, anaphylaxis, facial hirsutism, loss of scalp hair, hemorrhagic eruptions, and mental depression.

Clinical trials have demonstrated that progestogens reduce HDL levels, while natural progesterone levels have no effect on HDL levels. (15) Other side-effects include an increase in PMS symptoms, caused by relatively increased levels of circulating estrogen, increased sodium retention (16,17), and increased weight.

The newest, third generation oral contraceptives (OC's) contain the progestogens desogestrel or gestodene. These newest progestogens have been shown to elevate the risk of venous thrombosis. For women taking desogestrel or gestodene, the risk of pulmonary embolism is 30 in 100,000, twice the risk of women taking the second generation OC's. The risk is higher still for women who have never been pregnant or who carry factor V Leiden mutation, a genetic mutation resulting in resistance to Protein C, a natural anticoagulant. The risk returns to normal shortly after stopping the medication. Of these new, third generation progestogens, only desogestrel, compounded in Desogen and Ortho-Cept, is marketed in the U.S. (18)

ESTROGEN

The ovaries and to a lesser extent the adrenal glands secrete estrogen in a woman's body. The adrenal glands secrete very small amounts of estrogen; however, some adrenal androgen is converted to estrogen in the blood and peripheral tissues. The ovaries secrete estrogen during the follicular phase of menstruation in response to the anterior pituitary hormones LH and FSH. Estrogen levels increase from the end of menstruation through days 12-13. During this time, estrogen stimulates epithelial cell growth in the basal layer of the endometrium. In addition, vascular tissue, and spiral arteries and veins proliferate during this phase of estrogen increase. Estrogen levels peak then drop around day 13 of the menstrual cycle. At day 14 (in a 28 day cycle), the ovary releases the ovum, following which estrogen levels drop more gradually until the onset of menstruation.

Estrogen exists in three forms in the body:

E1, Estrone - converted from estradiol in the liver. Estrone is synthesized from progesterone and DHEA. The most carcinogenic form of estrogen, estrone (E1) increases after menopause, when the adrenal glands play a more prominent role in hormone synthesis than do the ovaries.

E2, Estradiol - Synthesized in the ovaries and metabolized in the liver, estradiol is the most active form of estrogen. Orally administered estradiol is converted into estrone in the small intestine. Increased estradiol levels are linked with increased risk of breast and endometrial cancer.

E3, Estriol - is a short acting estrogen and has weaker effect than estradiol or estrone. Estriol remains intact when supplemented orally, i.e., estriol is *not* converted into estrone, as is true with estradiol supplementation. Because estriol competes with estrone (E1) for receptor uptake when given in large or repeated doses, it has an anti-estrogenic effect. Estriol doses must be increased up to three times the dose of estradiol to achieve similar effects (e.g., reducing vasomotor flushes and vaginal dryness in menopausal women). In Europe and China, estriol is the preferred form of estrogen for HRT.

Estriol has been shown to be protective against breast cancer. The uterus secretes high levels of estriol during pregnancy, which may explain why women who have babies before age 22 have lower breast cancer rates — these women's estriol "set point" presumably is higher than those who give birth later in life. (19) Estriol binds to estrogen receptors and has a weaker effect than estradiol, thereby essentially mimicking the action of Tamoxifen, a drug prescribed to treat breast cancer, and experimentally now for breast cancer prevention in ostensibly high risk women. Estriol, however, does not increase the risk of endometrial cancer as does the drug Tamoxifen which increases the risk of endometrial cancer by seven and a half times, as reported by Bernard Fisher, MD, former head of the National Surgical Adjuvant Breast and Bowel Project. (20)

Studies of women in Japan, a population with a notably low incidence of breast cancer, demonstrated increased urinary metabolites of estriol compared to the control group of British women, again underlining the connection between increased estriol levels and decreased breast cancer rates. (21) Presumably, increased soy levels in Japanese women's diets may account for the increase in estriol levels. In an unpublished study by Lemon, Foley, and Kessinger, postmenopausal women with breast carcinoma and metastases received 2.5 - 15 mg of estriol to test the effects of estrogen on this population. They did not intend to administer the estriol for therapeutic purposes, yet 37% of the women in the study had remission or arrest of metastatic lesions. "The researchers proposed a long-time prospective study of estriol as a cancer preventive." (22)

FORMS OF ESTROGEN SUPPLEMENTATION

Oral: As mentioned earlier, much of the oral estradiol (E2) converts to estrone (E1) in the small intestine. The estrogen is carried to the liver via the portal vein, where the liver converts 35-95% of the estrogen into estrone-3-glucuronide. Oral estriol (E3) passes across the intestinal mucosa intact.

Transdermal: Transdermal application of estrogens, in the form of a cream or patch, avoids the conversion of estradiol into estrone in the small intestine, and also avoids the first pass through the liver. More estrogen circulates first through the body, with a smaller concentration reaching the liver, thereby reducing the common side-effect of gallbladder disease. The reduced amounts of estrogen that reach the liver, however, diminish the beneficial effects of estrogen on cholesterol levels (increased HDL levels). Transdermal application results in lower blood levels of estrogen than oral supplementation. Recent studies show that transdermal estrogen prevents bone loss, but transdermal application does not increase calcitriol (1/25 dihydroxy vitamin D) levels as does oral estradiol. Presumably transdermal estrogen arrests bone loss through another, unspecified mechanism. (23)

Transdermal patches should not be prescribed for postmenopausal women with uterine fibroids. A randomized trial demonstrated that after the first year of HRT, menopausal women with fibroids receiving conjugated equine estrogen (Premarin p.o.) with 2.5 mg MPA (Provera) showed no growth in fibroid tumor size, while those receiving 50 micrograms transdermal E2 plus 5 mg of MPA had significant increase in the tumor size. The transdermal estrogen patch is not a good HRT choice for menopausal women with a history of fibroids. (24)

Subcutaneous implant: This supplementation method was designed for women who require higher plasma levels of estrogen. Estradiol levels rise rapidly, remain constant for about four months, and then decline. "If reimplantation occurs, some women then rebound with supraphysiological levels which do not maintain for long periods. Symptom-free intervals become shorter and shorter and new implants become less and less effective. Another problem is that plasma estradiol levels can remain high for as long as 3 to 4 years after the implant has been removed. Essentially, she will be receiving unopposed estrogen unless progestogen therapy is applied." (25)

TESTOSTERONE

The adrenal glands are the primary source of testosterone in a woman's body. Testosterone levels remain relatively constant throughout a woman's life. At menopause, when estrogen and progesterone production dramatically decrease, testosterone production remains unchanged. The relative increase in testosterone accounts in part for hirsutism and other "masculinizing" effects associated with menopause.

Deficiency of testosterone in males has been linked with osteoporosis (26), and recent research has explored the role of testosterone in increasing bone mineral density in women. Researchers followed 20 women who had received long-term oral estrogen replacement. Ten received estradiol and testosterone implants, while the remaining 10 continued oral estrogens. The women with estradiol and testosterone implants had significant increases in bone mineral density (5.77% at the spine and 5.27% at the neck of the femur), while those continuing oral estrogen therapy showed no change in bone mineral density. (27) The researchers concluded that the combination of estradiol and testosterone implants would increase bone mineral density, even after years of oral estrogen replacement therapy.

As mentioned above, testosterone is more similar to progesterone than estrogen in its molecular structure, which may in part account for both progesterone and testosterone's ability to increase bone mineral density in postmenopausal women.

Testosterone also may be linked with a decreased risk of ovarian cancer. *In vitro* studies demonstrate that testosterone and androstenedione, but not cortisol, inhibit proliferation of ovarian tumor cells by a mechanism that is independent of steroid receptors. These androgens are secreted by the human ovary, primarily by the stromal cell compartment in menopausal women. The researchers hypothesize that relatively high local concentrations of ovarian androgens in vivo suppress ovarian epithelial carcinoma in women. If the androgens do indeed suppress ovarian carcinoma, the development of this cancer may be related to a failure to produce adequate levels of androgen in the postmenopausal ovary. (28)

HORMONAL EFFECTS ON SPECIFIC CONDITIONS

OSTEOPOROSIS

As mentioned above, estrogen, testosterone, and natural progesterone all affect bone mineral density (BMD). One of the major reasons cited for promoting HRT has been to increase bone density in peri- and postmenopausal women. Several studies demonstrate that women taking estrogen maintain, and sometimes increase, bone density in comparison with women who do not take HRT. The greatest loss in bone density occurs during the first 1-2 years of menopause. After that time, the bone loss rates of women on HRT versus those who do not take hormones are very similar. For women who use estrogen replacement therapy and then stop, their bone mineral loss is *greater* than average. (29) Women on HRT who take estrogen plus progestin continuously (steady dosages of estrogen and progestin) have increased BMD compared with women who take a cyclical regimen of the same hormones. (30)

Very few women, however, still take HRT in their 70's and 80's, which is precisely the time women are at greatest risk for falls and fractures. A physician prescribes HRT with the hope that the woman will continue to take the hormones for the rest of her life, which has proven to be a wildly optimistic assumption. Most women take HRT for an average of two years, not the recommended minimum of ten years. For the woman who continues HRT for ten years, she still has not reached the critical age when most fractures occur. Researchers following women with an average age of 76 in the Framingham Study found that if women stop taking HRT after a decade, their bone density falls, and they are more vulnerable precisely at the time when estrogen would be most helpful. (31)

Another study compared bone loss in the hip and calcaneus in women taking HRT as compared to those not taking HRT. Overall, the women showed a steady increase in bone loss, but current estrogen users had a 33% lower age-adjusted mean rate of bone loss in the hip, and 35% lower bone loss in the

calcaneus. (32) A study conducted by Duke University suggests that socioeconomic factors have the greatest impact on determining HRT use. Younger, more affluent white women living in urban areas were more likely to use estrogen than older women, especially African-American women. (33) Most women are at higher risk for fractures in their 70's and 80's, long after the ten years of recommended estrogen supplementation, assuming that the average onset of menopause is age 45-55.

Perhaps a more effective strategy for osteoporosis prevention would be to encourage HRT in perimenopausal women who are at high risk for osteoporosis, and to wait until the seventh decade for women who are low to medium risk for osteoporosis. Recent studies demonstrate that both estrogen and natural hormone supplementation will increase bone mineral density in older women (34,35), not only in perimenopausal women, as was assumed previously.

John R. Lee, MD points out that progesterone has been seriously overlooked in the discussions of HRT for osteoporosis prevention and reversal. "The case for using progesterone for osteoporosis is especially strong: estrogen has been shown to be only minimally effective in osteoporosis and is fraught with undesirable side effects. Osteoporosis results when either progesterone or testosterone is deficient. Progesterone and testosterone are molecularly similar and both are bone builders, i.e., stimulate osteoblasts. It would seem obvious that progesterone is the agent of choice for bone building in females. We should be taking our lead from common sense and the proper understanding of molecular specificity." (36)

Another less studied hormone that has been shown to affect bone mineralization is DHEA-S. Researchers discovered a positive correlation between bone mineral density and serum levels of DHEA-S, but found no correlation between bone density and serum estradiol levels. The findings suggest aromatase (P450 AROM) converts adrenal androgen, DHEA, to estradiol (E2) in osteoblasts. Aromatase is positively regulated by glucocorticoid and 1-alpha, 25-hydroxyvitamin D3. The researchers conclude that DHEA levels are an important factor in maintaining bone mineral density after menopause. (37)

In evaluating risks for osteoporosis, two conditions commonly overlooked are a history of thyrotoxicosis or major depression. Patients with a previous history of thyrotoxicosis and L-T4 therapy often have reduced femoral and lumbar vertebral BMD, which can be reversed by estrogen replacement therapy. (38) Major depression is associated with hypercorticoidism, which is a risk factor for osteoporosis. One study compared the BMD of trabecular bone in the lumbar vertebrae of 80 depressed inpatients older than 40 years with bone mineralization of lumbar vertebrae in 57 healthy subjects. An analysis of covariance model with age as a covariate showed that depressed patients had lower values of BMD. Other factors could not explain the findings, and the researchers concluded that major depression is a significant risk factor for osteoporosis. (39)

Heart Disease

Research has demonstrated that estrogen replacement therapy relaxes smooth muscles in the arteries (40), and increases both overall cholesterol levels and HDL levels. Estrogen replacement therapy, however, increases risk of embolisms for women who smoke, even as few as four cigarettes a day, or are exposed to secondary smoke. According to recent findings from the Postmenopausal Estrogen/Progestins Intervention (PEPI) Trials, while estrogen therapy increases HDL and reduces fibrinogen, ". . . there is only suggestive evidence that it actually prevents heart attacks." (41)

Menopause and Hormone Replacement Therapy (HRT)

While much of the preceding information pertains to peri- and postmenopausal women, this writing has not addressed some specific issues related to menopause and HRT. While conventional western medical science has labeled menopause a disease of "hormone deficiency," other cultures view menopause as a natural rite of passage into a time of greater wisdom and power. In a culture with a positive approach to aging in general, and to menopause in particular, women experience far fewer climacteric symptoms. (42) An important part of "curing" menopausal symptoms rests in redefining the role of elder women in our contemporary culture.

Some potential side-effects of estrogen replacement therapy not mentioned above include increased risk of adult onset asthma, systemic lupus erythematosus (SLE), and endometrial cancer. One study demonstrated that postmenopausal women who had never used HRT had a significantly lower age-adjusted risk of asthma than premenopausal women. Women who had ever taken estrogen HRT for more than ten years had twice the age-adjusted risk for developing asthma compared to those who had never taken estrogen, while current users had a positive correlation between daily dose and asthma risk. (43)

In order to assess the correlation between estrogen replacement therapy and development of SLE, a prospective cohort study of 69,435 women aged 30-55 years old compared past, current, and never users of estrogen replacement therapy. With never-users as the reference group, age-adjusted relative risks for SLE were 2.1 for those who had ever used estrogen replacement therapy (ERT), 2.5 for current users, and 1.8 for past users. The risk increased proportionately with the duration of postmenopausal hormone use. (44)

The addition of progestogens to estrogen replacement therapy reduces the risk of both adenomatous and atypical endometrial hyperplasia. (45) Progestogens, however, do not protect against breast cancer, although natural progesterone reduces the risk of breast cancer for women who are taking HRT.

For an excellent review of women's risk levels and potential need for HRT, refer to Tori Hudson ND's article, "Menopause: Establishing Risk Factors & Therapeutic Decision-Making" in the November 1994 *Townsend Letter For Doctors.*

Conclusion

Estrogen, progesterone, and testosterone, the three major gonadal hormones, are extremely potent messengers in the body, producing a wide range of effects in multiple systems and organs. Hormonal supplementation should be approached carefully after assessing a woman's symptoms and risk factors. Certainly not all women need HRT, but for those who do, consider natural progesterone therapy first, then evaluate the need for estrogen supplementation. Progestin therapy does not evoke the full range of effects that natural progesterone does, and may actually cause undesirable side effects. Estriol is

probably the safest of the three forms of estrogen for HRT, and is the estrogen source most commonly prescribed in China and Europe. For extreme menopausal symptoms, and/or severe osteoporosis, consider testosterone supplementation.

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