"Natural" Isomolecular Hormone Replacement: An Evidence-Based Medicine Approach

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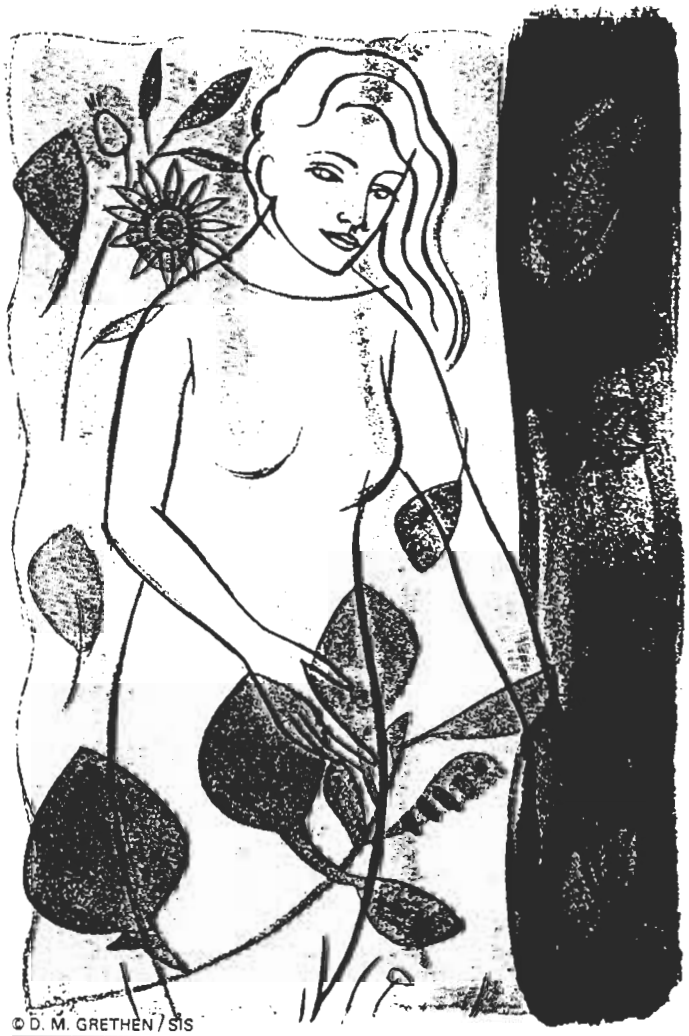

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Introduction

By current estimates, 1 of 5 persons in the world will be elderly by the year 2050. Some calculations indicate that in the next 20 years, the mean life expectancy may approach 85 to 90 years.[1] In the United States, there is an increasing elderly population.[2] There will be an even more dramatic increase between 2010 and 2030, when the "baby boom" generation reaches 65 years of age.[3] The number of women older than 45 years will exceed 700 million in the year 2000.[2] A significant number of women will experience menopause during those years and will seek ways of preventing the untoward effects of aging and illness. Those mushrooming numbers will significantly affect future health care costs and trends in healthcare management.

Menopause has a major impact on a woman's health and quality of life by causing a decrease in naturally occurring hormones. Menopause marks the beginning of a new phase in a woman's life that is relatively unencumbered by prior obligations. For many women, the postmenopausal phase of life is a time of many new opportunities.[4] A recent survey[5] indicated that women overwhelmingly view the postmenopausal period as the most happy and fulfilled period of their life.

The Benefits of Hormone Replacement Therapy

Hormone replacement therapy (HRT) is an important component in any preventive health program for the menopausal years. HRT produces great short-term benefit by relieving vasomotor and other symptomatic changes related to menopause. However, the real benefit provided by HRT is the long-term prevention of major health issues related to declining hormone levels. The prevention of cardiovascular disease (CVD) and osteoporosis has a significant effect on the quality of many women's lives, as well as on the burgeoning medical costs associated with increasing morbidity and mortality caused by those conditions.

Cardiovascular Disease

CVD, which includes coronary heart disease, cerebral vascular disease, and peripheral vascular disease, is the most common cause of death in women in the United States. An estimated 500,000 women die each year of CVD.[6] HRT helps to prevent CVD in postmenopausal women, and this may be its greatest benefit.

It is believed that the naturally circulating levels of hormones in the premenopausal years are cardioprotective because of a wide array of interconnecting factors. Premenopausal women exhibit higher levels of high-density lipoprotein cholesterol (HDL) and lower levels of low-density lipoprotein cholesterol (LDL) than those of their postmenopausal counterparts. After menopause, the LDL level increases rapidly, and the level of HDL decreases gradually in most women. During that time period, the risk of CVD doubles for women.

The favorable effect of estrogen replacement on lipid profiles may

be a biologically plausible mechanism of cardioprotection. Unopposed estrogen replacement increases the HDL level (which may be associated with cardiovascular benefit) and decreases the LDL level in women. Different progesterone preparations added to these regimens are problematic because they blunt the effect of estrogen on the increase in HDL.

Results of the Postmenopausal Estrogen/Progestin Intervention (PEPI) Trial[7] indicated that the most significant loss of benefit caused by the dampening of the increase in the HDL level was related to the addition of medroxyprogesterone acetate (MPA) to conjugated equine estrogen (CEE). The addition of micronized progesterone ("natural" or isomolecular hormone) was also evaluated in the PEPI Trial. Results indicated that micronized progesterone had less of a blunting effect on the level of HDL when compared with that produced by MPA. However, the PEPI Trial indicated that the use of either estrogen alone or estrogen-progesterone combinations were beneficial in improving lipid profiles when compared with the effects of using no HRT during the postmenopausal period.

Another benefit related to cardioprotection is the prevention of central truncal obesity that occurs as a result of aging. Preventing truncal obesity could inhibit or blunt the development of syndrome X, which is associated with abdominal adiposity, hyperinsulinemia, insulin resistance, and an atherogenic lipid profile.[8]

HRT is a significant benefit in the management of CVD during the postmenopausal period. The benefits are maintained for the duration of therapy. With ongoing HRT, a continuing increase in HDL and a decrease in LDL occur. Those beneficial changes are reversed when therapy is terminated.[9]

Osteoporosis

Osteoporosis is epidemic in the United States; more than 20 million individuals are affected.[10] It is a silent disease that produces no early symptoms indicative of low bone mass. The condition often remains undiagnosed until fracture occurs.

The accelerated bone loss that occurs during the menopausal period is widely recognized. This bone loss results from a combination of an increase in bone resorption and the slowing of bone formation. That pattern, which is related to the decreasing hormonal secretion that occurs during menopause, leads to significant morbidity and mortality. Bone loss is attributed to the effect of estrogen on osteoclasts[11] and to that of progesterone on osteoblasts.[12, 13]

Osteoporosis is the leading cause of fracture in elderly women, and the incidence of fracture increases with age.[14] Morbidity associated with fracture is significant and has a major effect on the healthcare system and on the quality of life of the patient. It has been reported that $45.2 billion total direct medical costs can be expected through 2005 as a result of treatment for hip fractures alone.[14] The incidence of death after hip fracture has been estimated to be between 12% and 40% in the first 6 months; an additional 12% to 20% of those patients die within the first year after fracture.[14] Of those who survive the first year, as many as 25% require care in long-term facilities, and half of those who remain at home experience reduced mobility that necessitates assisted-living care.[14]

It is also well known that HRT prevents bone loss during and after menopause. Studies[15] have identified the effectiveness of HRT in reducing fracture during the menopausal period. The duration of therapy is important in diminishing the risk of fracture caused by osteoporosis.

The increasing number of individuals with osteoporosis is related to the increasing number of elderly in our population. Increasing bone loss is related to hormone loss and also to increases in sedentary lifestyle, decreased physical activity, and decreased parity. In addition, deleterious dietary changes that occur with advancing age, including decreased protein consumption and decreased vitamin and mineral ingestion, can accelerate bone loss. Also of importance is the increase in the number of women smoking tobacco and drinking alcohol, both of which have a profoundly negative impact on bone maintenance.

It is beyond the scope of this review to mention all benefits related to HRT. Quality-of-life issues are of prime consideration, however. The symptomatic complaints that are related to decreasing levels of estrogen and progesterone include vasomotor instability (hot flashes and night sweats), insomnia, and increasing incidences of anxiety, emotional lability, and depression. In addition, women complain of increasing incidences of dyspareunia and pruritis, both of which can be caused by vaginal atrophy. Urinary frequency, discomfort, and incontinence that are related to the mucosal atrophy of the urinary tract may occur. HRT relieves those complaints in most women.[4]

Compliance

The benefits of taking HRT are tremendous, yet women are often reluctant to commit themselves to long-term HRT. Noncompliance adversely affects long-term morbidity and mortality and the long-term management of healthcare dollars.

It is estimated that only 15% of eligible women use HRT, and the overall compliance rate is 30%.[16] A recent review[17] determined that of 2500 postmenopausal women, compliance with HRT was sporadic. Among patients who began to use HRT, 20% terminated therapy within 9 months and 20% to 30% did not have their initial prescriptions filled.[17] Some patients have reported[4,18] that they were not fully convinced of the benefits of HRT in relieving subjective complaints such as increased breast tenderness, weight gain, fluid retention, and emotional lability, but the primary reason for the discontinuation of therapy was the fear of cancer. Women often hear conflicting reports about the development of either breast cancer or endometrial cancer and subsequently become unsure about the decision to begin or to continue HRT.

Women physicians who are more informed and aware of the benefits of HRT are more compliant with therapy. According to one study,[19] the range of HRT use in women physicians was from 59.8% in women 40 to 49 years of age to 36.4% in those 60 to 70 years of age.

Isomolecular Triple Estrogen and Progesterone Hormone Replacement

Isomolecular micronized triple estrogen coupled with micronized progesterone is becoming the standard "natural" hormone replacement during perimenopause and after menopause. Women are reading about this therapy, hearing about it from friends and family members, and demanding it from their physicians. This form of combined therapy has been largely untested.

The basis for the formulation of triple estrogen and progesterone was initially made from the urinary excretion patterns in healthy fertile women. The subsequent change in the triple estrogen formulation was made after several years of serum measurements of the estrogen levels in normal fertile women.[20] Initially, the triple estrogen formulation, which was based on the urinary excretion patterns, was placed at 80% estriol (E_3), 10% estradiol (E_2), and 10% estrone (E_1). After the serum levels had been evaluated, the formulation was changed to 90% estriol (E_3), 7% estradiol (E_2), and 3% estrone (E_1).

Because of the results of various studies of replacement of estriol, estradiol, and estrone as single agents, it is felt that the combination of isomolecular triple estrogen in a total dose of 2.5 mg is analogous to 0.625 mg of conjugated equine estrogen (Premarin).[21] The dosing equivalent to 10 mg of MPA, which is the standard traditional progesterone, is felt to be 200 mg of micronized progesterone if given 10 to 15 days per month[7] and 100 mg if given 25 days per month.[22] The PEPI Trial[7] demonstrated that 200 mg of micronized progesterone given for only 12 days of the month was adequate to oppose the endometrial proliferative changes caused by Premarin. It is important to review the individual components of isomolecular triple estrogen therapy.

Estriol

Estriol is converted from estrone primarily in the liver. A very small amount is converted from estradiol, and an even smaller amount of estriol may be secreted directly from the ovaries.[21] Estriol has always been considered a weak estrogen or metabolite. When compared with estradiol, estriol has a 20% to 30% lesser affinity for the estrogen receptor in the cell. However, it is highly effective if the concentration is kept equivalent to that of estradiol and can produce similar biologic responses.[4]

One of the benefits of using a higher concentration of estriol in the isomolecular triple estrogen formulation is the finding indicated in multiple studies[21] that estriol is antineoplastic. Premenopausal, healthy, nonpregnant Asiatic women, in whom breast-cancer risk is slight compared with that in Caucasians, have uniformly high rates of urinary estriol excretion.[23] There have been reports that high endogenous estriol levels protect against the tumor-producing effects of estrone and estradiol.[24] One investigator who used 5 mg/day of estriol to treat breast cancer reported that "after more than 500 rat-years' observation of the anti-breast-cancer effects, ...estriol is found to be the most active protective estrogen."[25]

According to 1 study,[26] another proven benefit of estriol is the amelioration of vasomotor symptoms at doses ranging from 2 to 8 mg/day. Endometrial biopsy indicated that those doses did not induce endometrial hyperplasia. The patients studied demonstrated mild-to-moderate lowering of serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels.

The most controversial area for the use of estriol has been in the prevention of osteoporosis. There have been conflicting reports about the protective effects of estriol not used in combination with estradiol and estrone or progesterone. Some studies show maintenance and increase of bone mass; others demonstrate no benefit for bone maintenance from estriol used without other hormones.[27,28] This is the most compelling reason to combine estriol, with its many protective effects, with lesser amounts of estradiol, estrone, and progesterone to maintain bone. Estriol administration significantly benefits the lower genitourinary tract by improving incontinence, the urgency and frequency of urination, and vaginal dryness and discomfort. The urethra and distal vagina have a common embryologic origin from the urogenital sinus and are therefore susceptible to similar hormone stimulation.[29,30]

The effect of estriol on cardiac risk has also been somewhat equivocal. However, unlike conventional estrogen therapy, it does not seem to contribute to hypertension or thrombosis.[31,32]

Estradiol

The second most important component of isomolecular triple estrogen therapy is estradiol. Estradiol (E_2) is the main estrogen secreted by the ovaries but is also found in the complex biosynthesis pathways in the body to a total amount of 100 to 300 µg/day in fertile menstruating women.[4] By the postmenopausal period, the level has decreased to 10 to 20 pg/day, and estradiol is derived primarily via estrone conversion in peripheral tissues. Estradiol used as HRT is converted in the small bowel to estrone by the gut-associated cytochrome P-450 enzymes.[33]

Estradiol has wide use and acceptance in commercial preparations; Estrace given at a dose of 1 mg equals 0.625 mg Premarin. Estradiol protects against osteoporosis and cardiovascular disease during the postmenopausal period and increases the level of HDL cholesterol. It has variable effects on the endometrium; some studies[34] indicate that at higher doses, estradiol causes endometrial proliferation. There is good oral absorption. The negative effect of the solitary administration of estradiol is that higher levels appear to stimulate carcinoma of the breast and endometrium in some women. It appears that estradiol should be opposed by estriol, which is an estrogen receptor binder and modulator.[4,35]

Estrone

The final and smallest component in isomolecular triple estrogen therapy is estrone. It has wide use and acceptance in commercial preparations such as Orth-Est (Ortho Pharmaceutical Corporation, Raritan, New Jersey) and Ogen (Upjohn Company, Bridgewater, New Jersey). The equivalent dose of estrone to the standard 0.625

mg of Premarin is 0.75 mg. However, estrone is felt to be procarcinogenic in both the breast and the endometrium at those higher doses.[35, 36] Premarin has been used for many years by thousands of women to improve the quality of life in menopausal and postmenopausal years. It is the gold standard by which many estrogen replacement therapies are measured. Premarin was first collected from the urine of pregnant mares (hence the name) and is referred to as CEE. It can now be synthesized.

The major estrogenic components of CEE are 75% to 80% estrone (E_1), 6% to 15% equilin (an equine estrogen), and 5% to 19% estradiol (E_2). There are actually many metabolites and forms of equilin found in CEE, all of which have potent estrogenic effects.[37] Equilin and its metabolites are poorly metabolized by the cytochrome P-450 system and can produce a pronounced hepatic response.[38] Metabolites of equilin are also 8 times more potent as a uterotropic agent than equilin itself and are found circulating for longer periods of time.[39,40] One of the metabolites of equilin, equilenin, is highly cytotoxic and causes oxidative stress and DNA damage in the breast and uterine tissue.[41] If isomolecular triple estrogen therapy is found to be safe and efficacious, then it would be a viable alternative to treatment with CEE.

Progesterone

Progesterone is necessary to oppose the stimulatory effects of estrogen on the uterus. Isomolecular micronized progesterone is as effective as traditional progestins in opposing the effects of estrogen.[7,42] It also may be needed to promote healthy bone tissue as well as to protect it. Isomolecular progesterone probably exerts that effect by stimulating osteoblasts.[13] Progesterone is an important component of HRT during and after menopause.

Isomolecular micronized progesterone is more effective than synthetic progestins in correcting the postmenopausal cardiac changes related to HDL and LDL cholesterol. Although both progesterone and progestin blunt the beneficial effects of estrogen, the micronized progesterone did so to a much lesser degree.[7] In fact, the Heart and Estrogen/Progestin Replacement Study (HERS), in which only estrogen and MPA were evaluated, did not indicate that estrogen combined with MPA exerted a protective effect during the first year of therapy against cardiovascular disease after menopause.[43]

Another remarkable benefit of isomolecular progesterone is in the area of side effects. Subjective and objective findings indicate that isomolecular micronized progesterone, when compared with the synthetic progestins, is associated with improved liver function, less breast tenderness, less fluid retention, improved mood, and fewer complaints of headache.[44,45]

The oral route of progesterone administration has long been considered clinically ineffective because of reported poor gastrointestinal absorption and a short biologic half-life. However, studies[46] have demonstrated that isomolecular progesterone, when taken orally in the micronized form, is physiologically active. There is also evidence that this form of progesterone produces a significant increase in tissue progesterone concentrations in the myometrium, endometrium, and breast.[46] There have been reports[47] of significantly improved absorption of oral micronized progesterone given with a meal.

Synthetic progestins blunt the favorable effects of estrogen on the lipid profiles to a greater degree than does isomolecular progesterone.[7] The progestins also may stimulate breast cancer and are poorly metabolized by the cytochrome P-450 enzyme system.[18] It appears that isomolecular micronized progesterone is superior to synthetic progestins when used as HRT during and after menopause.

Delivery Forms

Until recently in the United States, isomolecular micronized triple estrogen and micronized progesterone were available only from compounding pharmacists, who acquire bulk pharmaceutical-grade powder and prepare it to the specifications of the prescribing physician. This has enabled the physician, with the help of the pharmacist, to tailor isomolecular hormone therapy to fit the patient's needs. The current preferred delivery route is an oral gelatin capsule of micronized powdered hormone mixed with either a slow-releasing agent or oil. Other routes of delivery prepared by the compounding pharmacist include lozenges (troches), rectal or vaginal suppositories, and topical creams.

Capsules

The pharmaceutical-grade powder of estrogen or progesterone can be milled to an ultrafine consistency termed "micronized."[46] The decrease in particle size that results from micronization can increase aqueous dissolution in the gastrointestinal tract and enhance absorption; thus the oral form of delivery via a gelatin capsule provides improved bioavailability. The micronized powder can be compounded with a slow-releasing agent such as methylcellulose to provide a prolonged, even delivery of the hormone. When micronized powder is suspended in polyunsaturated fatty acid oil, there is direct absorption via chylomicron formation into the lymphatics. This process bypasses some of the early hepatic clearance, which further enhances bioavailability.[34] This is the basis for the Solvay Pharmaceutical micronized progesterone product that is prepared in an oil base.

Lozenges

Lozenges (troches) are another common mode of delivery. The micronized hormone is suspended in a liquid medium, which is poured into a mold and allowed to become firm to form lozenges. A lozenge is held in the mouth between the lip and gum. The transmucosal absorption bypasses the cytochrome P-450 hepatic clearance and results in greater bioavailability of the isomolecular hormone. More than 50% of the lozenge is swallowed by the normal mechanism of saliva formation, and the remainder is absorbed transmucosally. There is less patient satisfaction with lozenges because of the length of time needed to hold the lozenge in the mouth until it has dissolved. This delivery form may be beneficial for patients that have poor absorption as a result of gastrointestinal disorders.

Suppositories

The hormones can also be delivered via a suppository that can be inserted into either the vagina or rectum. Multiple studies[48] have demonstrated that suppositories provide adequate absorption and blood levels of delivered hormones; however, patient satisfaction with that form of administration is less.

Transdermal Creams

The most controversial system of hormone delivery is the transdermal cream. The progesterone cream is the most widely available. There is a wide variety in the quality of progesterone creams found in health food stores and from mail order firms.[49] If the cream consists only of suspended wild yam extracts, there is no bioactive hormone in the cream. The wild Mexican yam must be manipulated in the laboratory to produce the bioactive hormone. Even with pharmaceutical-grade hormone, the bioavailability that results from the cream route of administration is questionable.[49] There is no clear evidence of how consistent the absorption and degradation of transdermal cream application are. Some reports[50] indicate that body fat acts as a depot for transdermally delivered hormones that escape normal hepatic degradation and may accumulate systemically. Because more effective dosing routes are available, hormone administration via transdermal cream should be avoided until additional studies clarify the absorption and disposal of topically applied hormonal creams.

Dosing Amount

Currently, the recommended dose of isomolecular triple estrogen is placed at 2.5 to 5.0 mg/day with the proportions of 90% estriol, 7% estradiol-17β, and 3% estrone. (Personal communication, Jonathan Wright, MD, fall 1998, Tahoma Clinic, Kent, Washington). This has been given as a twice-daily dose. The slow-release formulation used by compounding pharmacists yields fewer "peak-and-valley" blood levels when administered in capsule form.

There are no completed trials at this time that evaluate triple estrogen therapy. At the University of Kansas Medical Center, a double-blind, placebo-controlled pilot study comparing the effects of isomolecular micronized triple estrogen and micronized progesterone with those of traditional CEE and MPA in postmenopausal women is under way. The study will be completed in the year 2000. Studies on micronized progesterone have been more extensively published. The dose of micronized progesterone is placed at anywhere from 50 to 200 mg/day given as a twice-daily dose or as a single daily dose.[7] (Personal communication, Jonathan Wright, MD, fall 1998, Tahoma Clinic, Kent, Washington.)

The use of micronized progesterone is less controversial because it has been used for almost 20 years in Europe, it is a pharmaceutical preparation that has been approved by the Food and Drug Administration (Solvay Pharmaceuticals, Inc. Marietta, Georgia), and the results of the PEPI Trial have defined its use and effect.

Dosing Schedule

The dosing schedule for micronized progesterone has been extensively studied in Europe for almost 20 years. From 1980 through 1990, the dosing schedule was cyclic and sequential; that is, the estrogen and micronized progesterone were given for only part of the month. The estrogen was given for 21 to 25 days, and the progesterone was given for 6 to 10 days of the month at levels of 100 to 300 mg/day.[22] This initial dosing regimen was effective in preventing endometrial hyperplasia. However, induced regular bleeding in 80% of treated cycles proved to be a disadvantage that resulted in poor patient compliance.

From 1990 through 1995, European investigators continued the cyclic sequential administration of estrogen with micronized progesterone. They extended the duration of the progesterone dosing to 12 to 14 days and used 200 mg/day of micronized progesterone orally. This regimen was chronicled in prospective randomized studies,[22] the results of which indicated that although the endometrium and heart were properly protected and the incidence and duration of bleeding were less when micronized progesterone was used, the induced regular bleeding continued to be unacceptable.

In an attempt to eliminate the bleeding, the investigators evaluated a continuous combined delivery method. Estrogen was administered with 100 mg of micronized progesterone every day of the month to suppress bleeding. Unfortunately, it was soon discovered that from 35% to 70% of patients experienced some episodes of irregular bleeding on this schedule after a few months. In addition, hysteroscopic evaluation determined that abnormal angiogenesis occurred in spite of an atrophic or subatrophic endometrium.[22] There were also high dropout rates with this regimen, which was quickly abandoned.

The current regimen advanced in Europe after multiple studies and extensive experience is a cyclic combined dosing regimen. The estrogen is given with 100 mg of micronized progesterone each day for 25 days on a 28-day calendar. This regimen has been studied in more than 400,000 patients in Europe. The endometrium is maintained in an atrophic pattern; there is minimal bleeding, and 85% to 95% of patients are reported to be amenorrheal after the sixth month of the regimen.[22] There is no abnormal angiogenesis. The dropout rate is reported to be 5% to 11%. Fewer subjective complaints have been reported. As a result of this extensive European experience and the experience of practitioners of complementary and alternative medicine in the United States, the dosing schedule may be best placed at a 25-day combined regimen of isomolecular micronized triple estrogen and micronized progesterone based on a 28-day calendar. The current recommendation for micronized triple estrogen should begin at the 2.5 mg/day dose based on 90% estriol, 7% estradiol, and 3% estrone divided in a twice-daily dose. The micronized progesterone should be given at a range of 100 to 200 mg/day with food and can be given as a twice-daily or single dose. The hormone can be compounded with a slow-release formula or administered in an oil base.

However, a large multicenter trial in the United States will be necessary to assess whether an isomolecular micronized triple estrogen and progesterone regimen protects against osteoporosis, maintains the endometrium without hyperplasia, protects against cardiovascular disease, and is well-tolerated at those doses by most women. There is compelling evidence from the literature to support those hypotheses.

References

1. Olshansky SJ, Carnes BA, Cassel C. In search of Methuselah: Estimating the upper limits to human longevity. *Science.* 1990;250:634-640.
2. Diczfalusy E. Menopause, developing countries and the 21st century. *Acta Obstet Gynecol Scand Suppl.*1986;134:45-57.
3. Manton KG, Soldo BJ. Dynamics of health change in the oldest old: New perspectives and evidence. *Health Soc.* 1985;63:206-285.
4. Speroff L, ed. *Clinical Gynecology Endocrinology and Infertility.* 5th ed. Baltimore, MD: Williams & Wilkins; 1994.
5. Kaufert P, Boggs PP, Ettinger B, et al. Women and menopause: Beliefs, attitudes, and behaviors. The North American Menopause Society 1997 Menopause Survey. *Menopause.* 1998;5:197-202.
6. Wenger NK, Speroff L, Packard B. Cardiovascular health and disease in women. *N Engl J Med.* 1993;329:247-256.
7. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. *JAMA.* 1995;273:199-208.
8. Haarbo J, Marslew U, Gotfredsen A, et al. Postmenopausal hormone replacement therapy prevents central distribution of body fat after menopause. *Metabolism.* 1991;40:1323-1326.
9. Granfone A, Campos H, McNamara JR, et al. Effects of estrogen replacement on plasma lipoproteins and apolipoproteins in postmenopausal, dyslipidemic women. *Metabolism.* 1992;41:1193-1198.
10. Dempster DW, Lindsay R. Pathogenesis of osteoporosis. *Lancet.* 1993;341:797-801.
11. Ettinger B, Genant HK, Steiger P, et al. Low-dose micronized 17 beta-estradiol prevents bone loss in postmenopausal women. *Am J Obstet Gynecol.* 1992;166:479-488.
12. Christiansen C, Riis BJ, Nilas L, et al. Uncoupling of bone formation and resorption by combined estrogen and progesterone therapy in postmenopausal osteoporosis. *Lancet.* 1985;2:800-801.
13. Prior JC. Progesterone as a bone-trophic hormone. *Endocr Rev.* 1990;11:386-398.
14. Lukert B, ed. *Practitioner Update on the Diagnosis and Treatment of Osteoporosis.* New York: Tufts University School of Medicine, SCP Communications; 1995.
15. Kiel DP, Felson DT, Anderson JJ, et al. Hip fracture and the use of estrogens in postmenopausal women: The Framingham Study. *N Engl J Med.* 1987;317:1169-1174.
16. Mazade P, ed. *The Menopause Hormone Therapy and Women's Health.* Washington, DC: US Government Printing Office. US Congress, Office of Technology Assessment; 1992.
17. Ravnikar VA. Compliance with hormone therapy. *Am J Obstet Gynecol.* 1987;156:1332-1334.
18. Colditz GA, Stampfer MJ, Willett WC, et al. Prospective study of estrogen replacement therapy and the risk of breast cancer in postmenopausal women. *JAMA.* 1990;264:2648-2653.
19. McNagny SE, Wenger NK, Frank E. Personal use of postmenopausal hormone replacement therapy by women physicians in the United States. *Ann Intern Med.* 1997;127:1093-1096.
20. Schliesman B, Robinson L. Serum estrogens: Quantitative analysis of the concentration of estriol compared to estradiol and estrone. Kent, WA: Meridian Valley Laboratory: 1997.
21. Follingstad A. Estriol, the forgotten estrogen? *JAMA.* 1978;239:29-30.
22. de Lignieres B, Driguez PC. Long-term experience with oral micronized progesterone and effects on the endometrium. *Contemporary OB/GYN.* September, 1998(suppl):10.
23. Bulbrook RD, Swain MC, Wang DY, et al. Breast cancer in Britain and Japan: Plasma oestradiol - 17β, oestrone and progesterone and their urinary metabolites in normal British and Japanese women. *Eur J Cancer.* 1976;12:725-735.
24. Lemon HM, Wotiz HH, Parsons L, et al. Reduced estriol excretion in patients with breast cancer prior to endocrine therapy. *JAMA.* 1966;196:1128-1136.
25. Lemon HM. Oestriol and prevention of breast cancer. *Lancet.* 1973;1:546-547.
26. Tzingounis VA, Aksu MF, Greenblatt RB. Estriol in the management of menopause. *JAMA.* 1978;239:1638-1641.
27. Devogelaer JP, Lecart C, Dupret P, et al. Long-term effects of percutaneous estradiol and estriol on bone loss and bone metabolism in postmenopausal women. *Maturitas.* 1998;28:243-249.
28. Itoi H, Minakami H, Sato I. Comparison of the long-term effects of oral estriol with the effects of conjugated estrogen, 1-alpha-hydroxyvitamin D3 and calcium lactate on vertebral bone loss in early menopausal women. *Maturitas.* 1997;28:11-17.
29. Iosif CS. Effects of protracted administration of estriol on the lower genitourinary tract in postmenopausal women. *Arch Gynecol Obstet.* 1992;251:115-120.
30. Melis GB, Cagnacci A, Bruni V, et al. Salmon calcitonin plus intravaginal estriol: An effective treatment for menopause. *Maturitis.* 1996;24:83-90.
31. Head KA. Estriol: Safety and efficacy. *Altern Med Rev.* 1998;3:101-113.
32. Schairer C, Adami HO, Hoover R, et al. Cause-specific mortality in women receiving hormone replacement therapy. *Epidemiology.* 1997;8:59-65.
33. Yen SS, Martin PL, Burnier NM, et al. Circulating estradiol, estrone and gonadotropin levels following administration of orally active 17β-estradiol in postmenopausal women. *J Clin Endocrinol Metab.* 1975;40:518-521.
34. Hargrove JT, Maxson WS, Wentz AC, et al. Menopausal hormone replacement therapy with continuous daily oral micronized estradiol and progesterone. *Obstet Gynecol.* 1989;73:606-612.
35. Lemon HM, Wotiz HH, Parsons L, et al. Reduced estriol excretion in patients with breast cancer prior to endocrine therapy. *JAMA.* 1966;196:1128-1136.
36. Fishman J, Fukushima DK, O'Connor J, et al. Low urinary estrogen glucuronides in women at risk for familial breast cancer. *Science.* 1979;204:1089-1091.
37. Bhavnani BR. Pharmokinetics and pharmodynamics of conjugated equine estrogen: Chemistry and metabolism. *Proc Soc Exp Biol Med.* 1998; 217:6-16.
38. Stumpf PG. Pharmacokinetics of estrogen. *Obstet Gynecol.* 1990;75(suppl 4):9S-14S.
39. Bhavnani BR, Gerulath AH. Metabolism of [3H] equilin in normal and malignant human endometrium and in endometrial adenocarcinoma transplanted into nude mice. *J Steroid Biochem Mol Biol.* 1991;38:433-439.
40. Bhavnani BR, Cecutti A. Metabolic clearance rate of equilin sulfate and its conversion to plasma equilin, conjugated and unconjugated equilenin, 17beta-dihydroequilin, and 17beta-dihydroequilenin in normal postmenopausal women and men under steady state conditions. *J Clin Endocrinol Metab.* 1993;77:1269-1274.
41. Zhang F, Chen Y, Pisha E, et al. The major metabolites of equilin, 4-hydroxyequilin, autoxidizes to an o-quinone which isomerizes to the potent cytotoxin 4-hydroequilenin-o-quinone. *Chem Res Toxicol.* 1999;12:204-213.
42. Kim S, Korhonen M, Wilborn W, et al. Antiproliferative effects of low-dose micronized progesterone. *Fertil Steril.* 1996;65:323-331.
43. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. *JAMA.* 1998;280:605-613.
44. Darj E, Axelsson O, Carlstrom K, et al. Liver metabolism during treatment with estradiol and natural progesterone. *Gynecol Endocrinol.* 1993; 7(2)111-114.
45. Dennerstein L, Spencer-Gardner C, Gotts G, et al. Progesterone and the premenstrual syndrome: A double blind crossover trial. *BMJ.* 1985;290: 1617-1621.
46. Maxson WS, Hargrove JT. Bioavailability of oral micronized progesterone. *Fertil Steril.* 1985;44: 622-626.
47. Simon JA. Micronized progesterone: Vaginal and oral uses. *Clin Obstet Gynecol.* 1995;38:902-914.
48. Kimzey LM, Gumowski J, Merriam GR, et al. Absorption of micronized progesterone from nonliquefying vaginal cream. *Fertil Steril.* 1991;56:995.
49. Cooper A, Spencer C, Whitehead MI, et al. Systemic absorption of progesterone from Progest cream in postmenopausal women [research letter]. *Lancet.* 1998;351:1255-1256.
50. Ilyia I, McLure D, Farhat MY. Topical progesterone cream application and overdosing. *J Altern Complement Med.* 1998;4:5-6.

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