Chapter 8

Current Status of Estrogen Therapy

Seung-Yup Ku, M.D., Ph.D.; and Seok Hyun Kim, M.D., Ph.D.
Dept of OB/GYN, College of Medicine, Seoul National University

ABSTRACT

Replacement of deficient hormones is an important axis of anti-aging medicine since aging is caused and manifested by various hormonal declines. Somatopause has been treated with growth hormone; andropause with testosterone; thyropause with thyroid hormones; and menopause with estrogen or other natural substances (including isoflavone and black cohosh), whereas facial flush, genital atrophy and other menopausal symptoms have been controlled with estrogen therapy (ET). Many studies have reported that ET helps to prevent cardiovascular disease, osteoporosis, and Alzheimer's disease. Recently, however, the increased risk of breast cancer and insignificant preventive effect of ET on cardiovascular disease was revealed by the Women's Health Initiative (WHI) study. Thus, it is appropriate to review the risks and benefits associated with ET when managing postmenopausal women. The efficacy of ET and natural estrogen surrogates in relieving postmenopausal symptoms will also be discussed. We will also consider the possible antioxidant properties of ET.

Keywords: menopause; Postmenopausal Estrogen Progestin Intervention (PEPI) Trial; The Women's Health Initiative (WHI) Study; Heart and Estrogen Replacement Study (HERS); North American Menopause Society (NAMS)

INTRODUCTION

The subject of estrogen therapy (ET) has become very controversial since the findings of the Women's Health Initiative (WHI) study. This paper will cover some of the basics of ET and relevant societies' guidelines and recommendations for its use.

The average human lifespan has increased dramatically over the last century, and recent projections expect this trend to continue for the foreseeable future. According to a recent report, the index of aging in Korea as of 2001 was 35%. Korean studies have revealed that the average lifespan of Korean women is approximately 78 years; this figure is projected to rise to 87 by 2010. The average woman usually outlives the average man by 7 to 8 years, and this is a significant social issue that has to be addressed.

MENOPAUSE

Despite significant increases in female life expectancy, the age of menopause has remained relatively constant. Therefore, the menopausal period has been growing since the 1950's. As can be seen in Figure 1, the women of today endure the symptoms and long-term complications of the menopause for 20 years or more of their life.

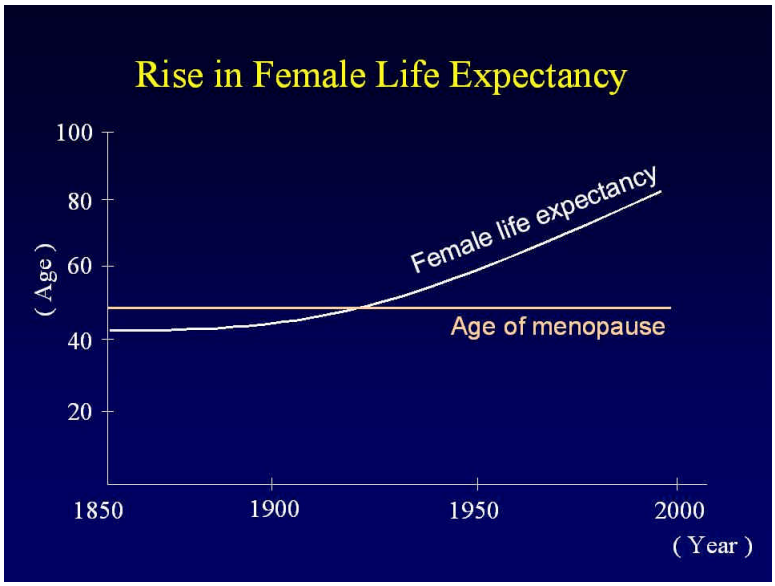

Figure 1. The rise in female life expectancy over the last 150 years, in comparison with the relative stability of the age of menopause.

Menopause means the stop of menstruation. It is accompanied by the decline of ovarian function, and typically occurs at around 50 years of age. Perimenopause usually begins in a woman's mid-40s and is indicated by irregular shortened menses. Because the transition from reproductive age to menopause, or climacteric, begins several years before menopause itself, anti-aging physicians and health practitioners should be concerned with the problems these women have much earlier than at the beginning of menopause.

The changes that occur at menopause include a decrease in reserve of follicles. Declining estradiol and inhibin levels lead to a rise in FSH levels, and the follicular phase becomes shorter. This means that follicles do not mature adequately. Together, this combination of events leads to luteal phase insufficiency, anovulation, oligomenorrhea (very light or infrequent menses), and eventually the cessation of menstruation.

The role of the anti-aging physician is to prevent or delay menopausal symptoms by keeping the risk of menopausal complications under the threshold level.

Symptoms of Menopause

As a woman enters into menopause, the cyclic FSH fluctuation disappears, and the increasing FSH levels accelerate follicle maturation. This acceleration shortens the menstrual period: this is the first sign of perimenopausal transition. The level of FSH is approximately 40 mlU/ml at menopause and can rise to as high as 100 mlU/ml within a year of menopause.

The symptoms of menopause include vasomotor symptoms such as hot flashes or night sweats: these symptoms tend to be more severe in women who smoke and those with a higher body mass; some women may also experience psychogenic manifestations such as depression. Other symptoms include genitourinary tract atrophy, skin and skeletal changes, and sexual symptoms.

Hot flashes are the most common menopausal symptom. They are experienced by 50% to 75% of women. The average duration is about 4 minutes, and the interval between episodes can vary from every few minutes to several days. Hot flashes, or night sweats, can cause sleep disturbance and this is thought to be at least partially responsible for psychogenic manifestations of menopause, such as depression, decreased concentration, and mood swings.

The genital atrophy that occurs with menopause results from the thinning of vaginal epithelium. In addition, vaginal rugae disappear, vaginal secretion decreases, and the vagina becomes short and narrow.

Vaginal sensation also decreases because of peripheral neuropathy. Women may also suffer with dyspareunia, leukorrhea, and occasionally vaginal spotting. Sexual problems may be caused by decreased lubrication.

Menopause causes atrophy of the urethral mucosa and a drop in urethral closure pressure. Together this can lead to a friable urethra. As such, postmenopausal women may experience urinary incontinence, burning sensation on urination, urgent and/or frequent need to urinate, and residual urine.

Lipid metabolism also changes with menopause. Postmenopausal women have higher LDL and lower HDL cholesterol levels, which increases their risk of cardiovascular disease. As can be seen in Figure 2, cardiovascular disease is the leading cause of death in Korea, and in many other countries including the USA. The increase in LDL cholesterol and drop in HDL cholesterol levels is caused by the decrease in estrogen levels that occurs at menopause. Every woman is exposed to the risk of cardiovascular disease in the postmenopausal period; however, these changes can be reversed by estrogen replacement. Without replacement, these metabolic changes may lead to the pathogenesis of atherosclerosis or coronary heart disease.

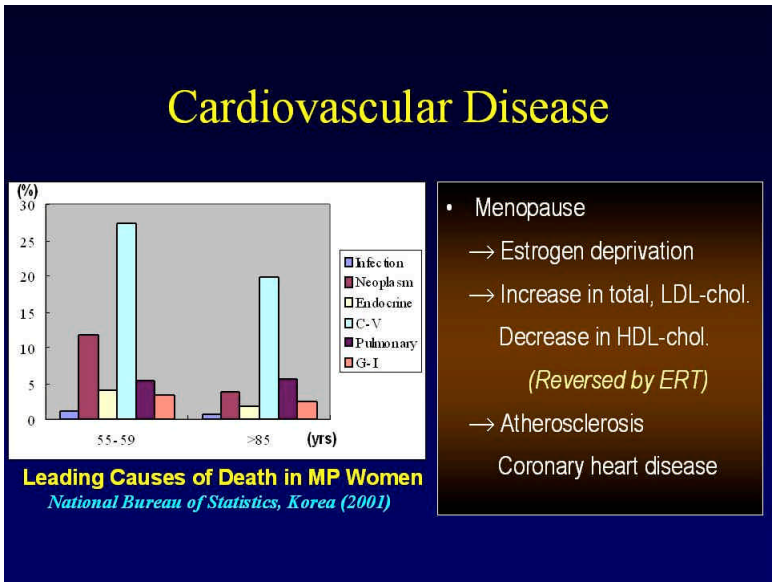

Figure 2. The leading causes of death among menopausal women in Korea, and how changes in lipid metabolism that occur at menopause lead to an increased risk of cardiovascular disease.

Bone metabolism is also affected by menopause. As a woman ages, her estrogen levels decrease and bone loss accelerates. Decreasing estrogen level leads to a decrease in calcium intake and absorption, thus serum ionized calcium levels drop. The resulting low levels of calcium stimulate the secretion of parathyroid hormone, and calcium is then mobilized from bone by excessive osteoclastic activity. The end result of this cascade of events is osteoporosis.

Postmenopausal women lose up to 5% of trabecular and 1% of cortical bone mass per year. The largest bone loss occurs in the first 8-10 years of menopause. Approximately 30% of postmenopausal women fall in the fast bone loser category; they lose more than 3% of bone mass per year. If a woman has an inadequate peak bone mass, her bone mineral content becomes less and less as time goes on, thus leaving her vulnerable to fractures.

ESTROGEN THERAPY

The use of ovarian extract was first suggested by Charles Edouard Brown-Sequard in 1889. Eight

years later, the first report on the effectiveness of ovarian extract for hot flushes was published. Estrogen was first isolated in 1929, progestin in 1934, and estradiol in 1936. Three years later, conjugated estrogen was isolated. Premarin was first used and approved in Canada in 1941, and in the USA one year later.

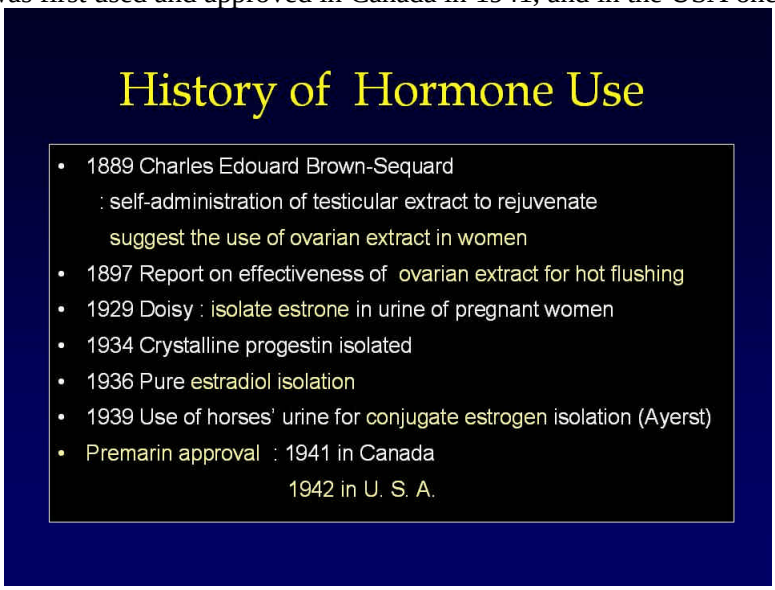

Figure 3. History of Hormone Replacement Therapy

Recent figures indicate that 46% of naturally postmenopausal women, and 71% of bilaterally oophorectomized women use ET in the USA. In Korea in 2002, these figures were 23% and 30%, respectively.

Estrogens and Progestins

There are two categories of estrogens, natural and synthetic. Some of the natural estrogens available include, conjugated equine estrogen (e.g. Premarin®), estradiol valerate, piperazine estrone sulfate (e.g. Ogen®), micronized estradiol, and 17ß-estradiol hemihydrate. Synthetic estrogens are not used for ET because of their side effects. The most common route of administration of estrogens is orally. However, there are also a number of methods of transvaginal and transdermal administration.

Progestins are prescribed for the purpose of endometrial protection. Both synthetic (for example, medroxyprogesterone acetate (MPA)) and norethisterone acetate, and natural progestins (for example, micronized progesterone) are used in combination with estrogen. Progestins can cause breast tenderness, bloating, agitation, depression, and PMS-like symptoms. These side effects are dependent upon the dose of progestin prescribed. Progestins do not interfere with estrogen's antioxidant activity or its ability to lower LDL cholesterol levels, and increase fibrinolysis. However, they are not without disadvantages, as they lower estrogen's ability to increase HDL cholesterol levels, dilate arteries, and increase cardiac inotrophic activity.

There are largely two combined estrogen and progestin therapies, sequential and continuous. Withdrawal bleeding will occur with sequential estrogen and progestin therapy, but not with continuous therapy. Combined estrogen and progestin therapy is not suitable for women without a uterus; therefore hysterectomized women should be given estrogen only.

Therapeutic Effects of Estrogen

Estrogen has a number of therapeutic effects, including:

- Relief of hot flashes and secondary psychiatric symptoms
- Improvement in genital atrophy

- Improvement of lipoprotein profiles
- Prevention of osteoporosis

Most women see an improvement in vasomotor symptoms such as hot flashes in a matter of weeks. However, it takes several months of treatment before bone mineral density begins to improve. Estrogen has also been thought to reduce the risk of cardiovascular disease and Alzheimer's disease; however, these benefits are controversial at present.

Estrogens and the Lipoprotein Profile

Estrogens exert a number of beneficial effects upon the lipoprotein profile. As well as raising HDL cholesterol levels and lowering LDL cholesterol levels, estrogens may have an anti-arteriosclerotic effect on arteries. They also increase fibrinolysis, enhance the action of vasodilators and antiplatelet aggregation factors, such as nitric oxide or prostacyclin, and have direct inotropic actions on the heart and large blood vessels. They also have antioxidant properties.

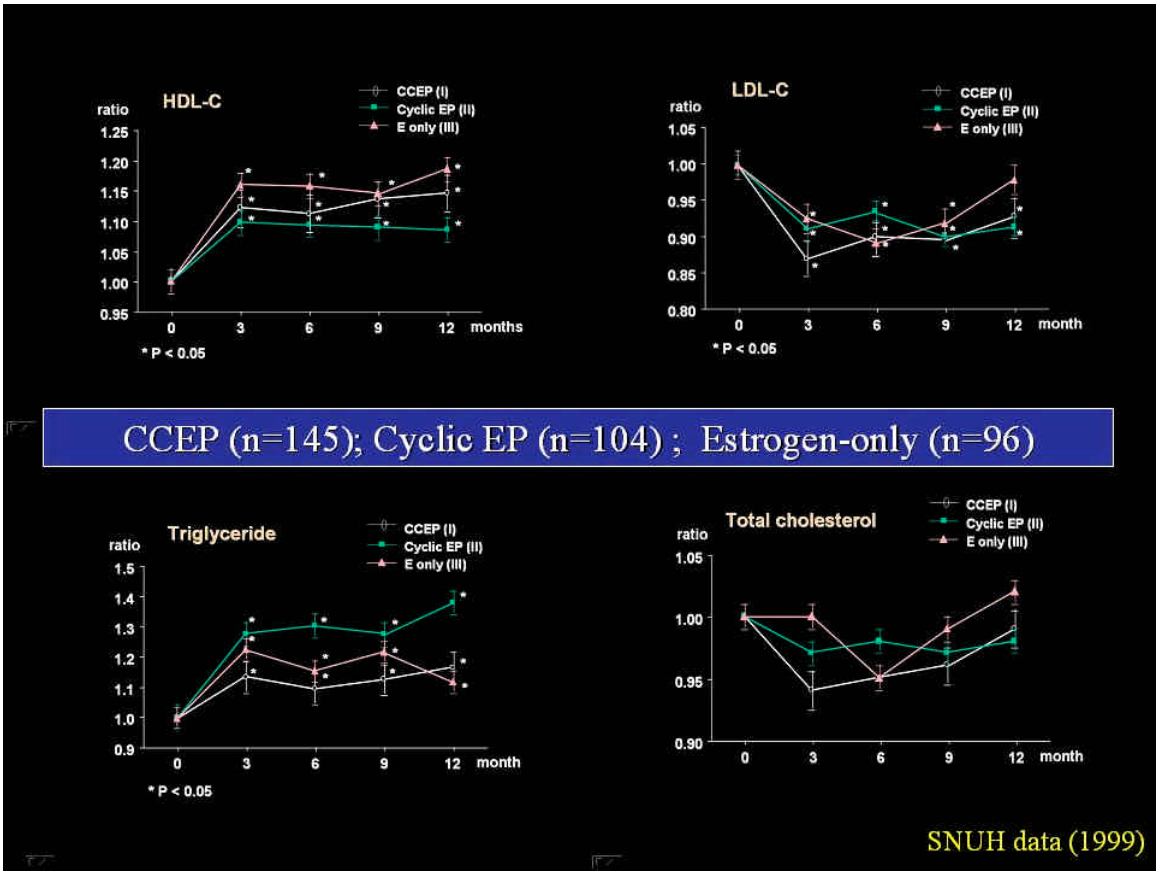

Figure 4. Effect of 7-12 months of ERT on the lipid profile of postmenopausal women. Data obtained from a study by Lee et al, Seoul National University, South Korea, 1999.

Figure 4 shows the results of a study conducted at Seoul National University, Korea, in 1999. For the study, the lipid profiles of postmenopausal women were measured before and after 7 to 12 months of estrogen replacement therapy. Three regimens were used: continuous combined estrogen/progestin in 145 women; sequential or cyclic estrogen/progestin in 104 women; and estrogen only therapy in 96 women. Results showed that ET led to a 10% to 20% increase in HDL cholesterol levels, and a decrease in LDL cholesterol levels and total cholesterol levels. However, treatment did slightly increase triglyceride levels.

Estrogen and Alzheimer's Disease

Research suggests that estrogen has a beneficial effect on the activities of daily living in women with Alzheimer's disease. In a recent Korean randomized controlled trial, Tacrine was given to 26 women, and conjugated equine estrogen (CEE) estrogen to 29 women. The treatment was continued for six months, and the changes before and after treatment were evaluated using a number of tests, including the mini-mental status examination (MMSE), the Hopkins's Verbal Learning Test, instrumental activities of daily living (IADL), and the Boston Naming Test. Interestingly enough, the results were the same for both groups, except that IADL rated more highly in the CEE group. The overall efficacy of estrogen was similar to Tacrine in terms of cognition and mood.

Contraindications and Complications of Estrogen Therapy

Estrogen replacement should not be started in women with a past history of myocardial infarction or cerebral vascular disease. ET is also contraindicated in women with depressed liver function and acute thromboembolism.

Unfortunately, there are a number of unwanted side effects associated with ET. These include: breast cancer, endometrial hyperplasia, endometrial carcinoma, dysfunctional uterine bleeding, gastrointestinal dysfunction, and thromboembolism.

Recent studies suggest that a significant number of women are quitting ET. A study by *Reynolds et al* revealed that 20% of women quit ET at the end of their first month; 50% at the end of their first year; and 65% at the end of two years. Furthermore, just 20% of women took ET for more than five years. The most common reasons for stopping ET were the unwanted side effects of estrogen and fear of cancer. Interestingly, women who were prescribed ET by a gynecologist were more likely to continue with the treatment. The authors suggested that gynecologists are more likely to prescribe regimens that cause minimal side effects, or they are more able to explain the risks and benefits of estrogen, thus these women are more likely to know what to expect from ET.

IMPORTANT CLINICAL TRIALS CONCERNED WITH ET

There have been many trials carried out on the efficacy and safety of ET. Here we will discuss the most important of those trials.

Postmenopausal Estrogen Progestin Intervention (PEPI) Trial

PEPI was one of the first representative studies of ET, and was published in 1995. It was conducted as a randomized, double-blind, placebo-controlled trial, and it lasted for three years. A total of 875 postmenopausal women from seven clinical centers were included in the trial. The regimens included sequential estrogen/progestin using medroxyprogesterone acetate (MPA) or micronized progesterone, continuous combined estrogen/progestin (CCEP) using MPA, estrogen only, and placebo.

Results showed that with regards to increasing HDL cholesterol levels, unopposed estrogen and sequential estrogen/progestin using micronized progesterone were superior to sequential estrogen/progestin using MPA. The decrease in LDL cholesterol levels was similar in all treatment groups. Decreases in fibrinogen levels and a favorable effect on fasting insulin and glucose levels were greater in all treatment groups compared to the placebo group.

The Women's Health Initiative (WHI) Study and the Heart and Estrogen Replacement Study (HERS)

The Women's Health Initiative (WHI) is a randomized, blind, placebo-controlled multicenter study sponsored by the National Institutes on Health (NIH). It began in 1993. Study subjects were healthy

postmenopausal women aged 50 to 79 years. CCEP was prescribed to 16,608 women and unopposed estrogen to 10,739 women. The follow-up period was five years. The CCEP arm of the trial was stopped in July 2002 when it was found that the treatment increased the risk of breast cancer to such an extent that it overweighed the benefits of treatment. The estrogen-only arm of the WHI has been just stopped and is pending its results; however, the results about breast cancer do not seem to be affected by ET.

HERS is another important randomized, blind, placebo-controlled trial. The study involved 2,763 postmenopausal women aged 55 to 79 with documented coronary heart disease. The women were treated with CCEP or an inactive placebo. The total follow-up period was 6.8 years.

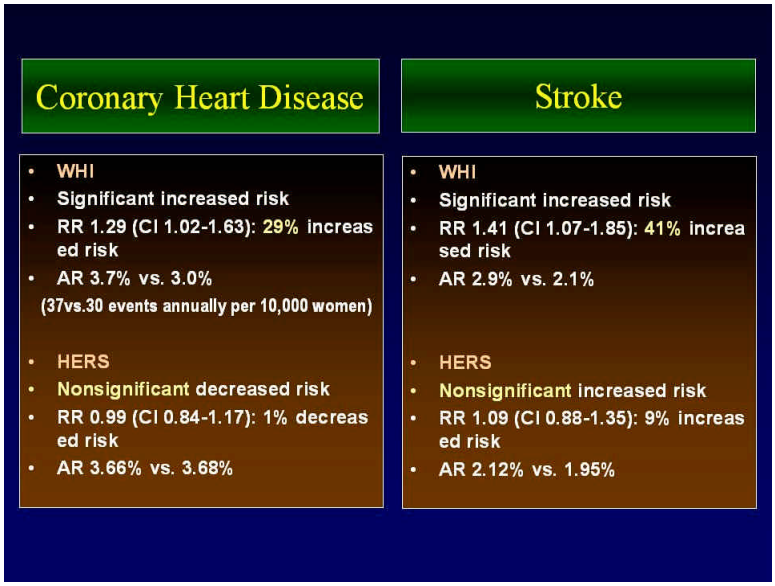

Figure 5. Comparison of results obtained from WHI study and HERS study; coronary heart disease and stroke.

Figure 5 shows that the two studies yielded conflicting results when determining the risk of coronary heart disease. The WHI reported that ET led to a 29% increase in relative risk, while HERS found that ET led to a nonsignificant decreased risk. As for stroke, the WHI showed a 41% increase in relative risk while HERS concluded that ET led to a nonsignificant increased risk of stroke. Both studies found that ET increases the risk of thromboembolism by more than 100%. Breast cancer risk was increased by 26% in the WHI study and 27% in HERS, though they were nonsignificant.

As shown in Figure 6, on the positive side, both studies found that estrogen is beneficial when it comes to colon cancer. The relative risk decreased by around 37% in the ERT group of WHI. However, the decrease in this risk was deemed nonsignificant in HERS. As for the risk of osteoporotic fracture, the WHI study showed a 24% decrease in risk, while HERS concluded that ERT led to a nonsignificant increased risk.

Many relevant academic bodies and researchers have questioned the appropriateness of the design of the WHI study. It is an important topic and clearly has to be investigated further.

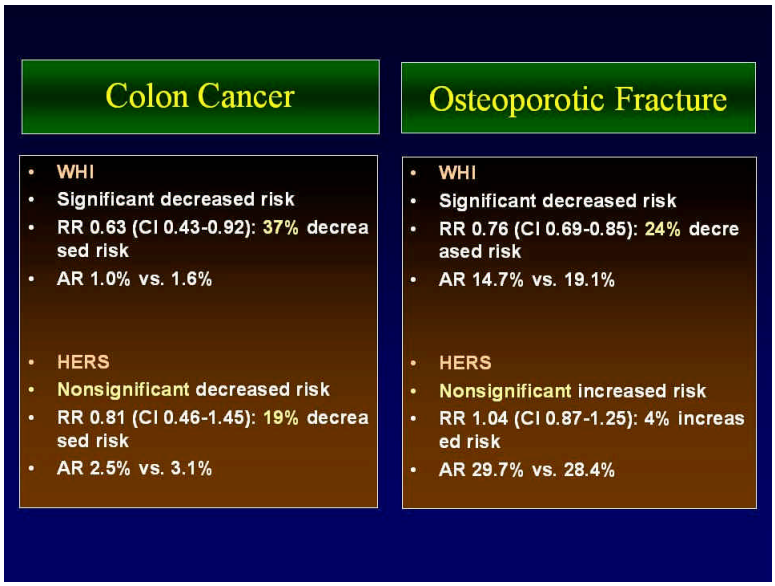

Figure 6. Comparison of results obtained from WHI study and HERS study: colon cancer and osteoporotic fracture.

Recommendations and Regulations Governing ET

The United States Preventive Services Task Force's (USPSTF) recommendations towards a certain service are presented in Figure 7. With regards to ET, the USPSTF recommends against the routine use of estrogen and progestin for the prevention of chronic conditions in postmenopausal women. That is the recommendation "D". Regarding unopposed estrogen, ET was designated as the "I" recommendation.

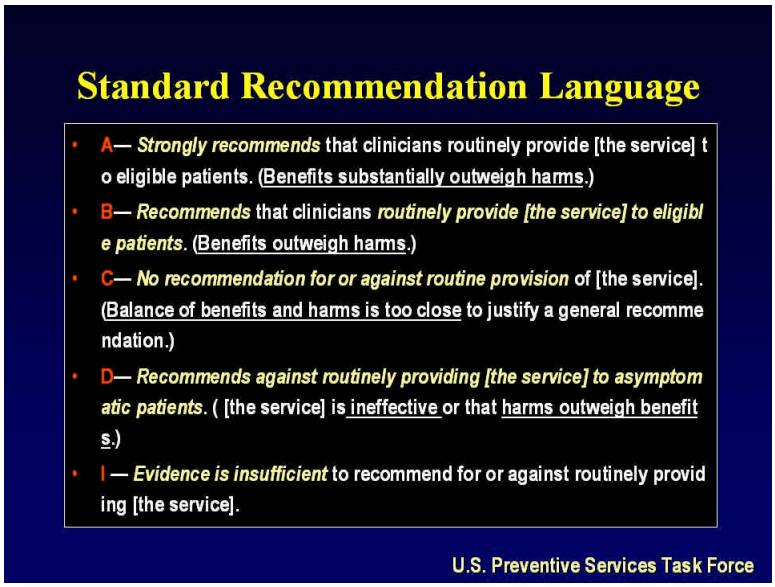

Figure 7. The United States Preventive Services Task Force (USPSTF) Recommendations

What about the US Food and Drug Administration (FDA)? Following results obtained in the WHI study, in February 2003 the FDA formulated new guidelines regarding safety warnings for all estrogen and estrogen with progestin products. Specifically, the new warning highlights the increased risks for heart disease, heart attacks, strokes, and breast cancer. It also emphasizes that these products are not approved

for heart disease prevention. The FDA also modified the approved indications for Premarin®, Prempro® and Premphase® to clarify that these drugs should be used only when the benefits clearly outweigh the risks.

The three postmenopausal indications for conjugate estrogens are:

1. Treatment of moderate to severe vasomotor symptoms of menopause, such as hot flashes: this indication has not changed.
2. Treatment of moderate to severe symptoms of vulvovaginal atrophy, such as vaginal dryness and irritation: when these products are being prescribed solely for the treatment of vulvovaginal atrophy, topical estrogen should be considered.
3. Prevention of postmenopausal osteoporosis: when estrogens are being prescribed only for the prevention of osteoporosis, non-estrogen treatment should be considered.

The revised contraindications of conjugate estrogens include: undiagnosed vaginal bleeding, known history of breast cancer or estrogen-dependent neoplasm, active deep venous thrombosis, pulmonary embolism, or recent arterial thromboembolic disease such as stroke or myocardial infarction. Cases of known hypersensitivity to the ingredients and known or suspected pregnancy are also contraindications for estrogen use.

The North American Menopause Society's recommendations for ET are shown in Figures 8 and 9.

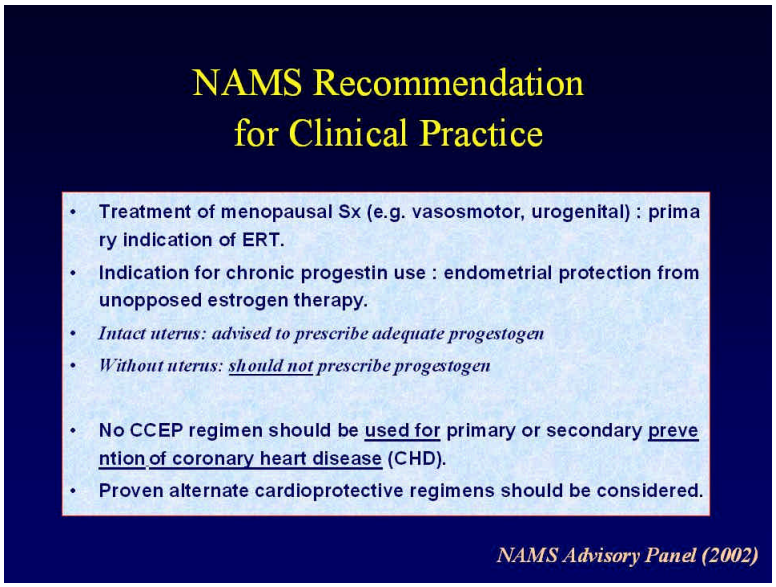

Figure 8. The North American Menopause Society Recommendations for ET, Part I.

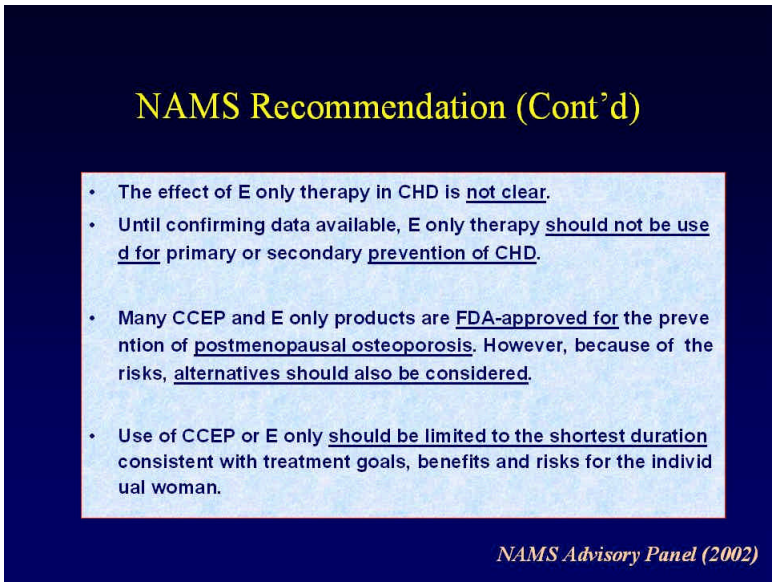

Figure 9. The North American Menopause Society Recommendations for ET, Part II.

Lowering the Dose of Estrogen

Estrogen causes several unwanted side effects. We need to know that ET will still be effective if we lower the dose enough to reduce the side-effects. The Women's Health Osteoporosis Progestin and Estrogen (HOPE) study was a randomized, double-blind, placebo-controlled trial of CEE and MPA. Eight hundred and twenty-two women participated in this study for two years. Participants were given either 0.625, 0.45, 0.3 mg per day of CEE plus either 2.5 or 1.5 mg per day of MPA. After two years of treatment bone density increased, and levels of serum osteocalcin (OC) and urinary crosslinked N-telopeptides of type I collagen (NTx), which are both biochemical markers of bone turnover, decreased in all treatment groups. Doses of less than 0.625 mg per day also effectively increased the BMD. As for the changes in lipid profiles, researchers reported that a lower dose of estrogen induced favorable changes in lipids, lipoproteins and hemostatic factors without affecting carbohydrate metabolism. Vasomotor symptoms and vaginal atrophy can also be treated effectively with a lower dose of estrogen.

ESTROGEN AND ANTI-AGING

The four major mechanisms for aging are methylation, glycation, inflammation, and oxidative stress. Estrogen may have several anti-aging effects. Here we will consider its homocysteine lowering properties, antioxidant action, and the relationship between ET and oxidative stress.

Increased levels of homocysteine is linked to an increased risk of cardiovascular disease. Methyl donors such as vitamin B-6, vitamin B-12, and folic acid are often used to decrease homocysteine levels. As has been noted, estrogen also has the ability to lower homocysteine levels. Results of one study revealed that 15 months of treatment with 1~2 mg of 17-beta estradiol led to a significant decrease in homocysteine levels. Thus, while homocysteine levels increase after menopause, these levels can be lowered by estrogen treatment.

Estrogen also appears to improve the metabolism of carbohydrates. Results of a study of postmenopausal women with type II diabetes revealed that short-term ET improved insulin resistance. The results also showed that ET led to a significant decrease in glycated hemoglobin and increased suppression of hepatic glucose production by insulin.

With regards to inflammation, we have indirect evidence about the action of estrogen. A

randomized, controlled trial by *Hall et al* found that ERT improved the symptoms of rheumatoid arthritis. 50 μg per day of transdermal estradiol was given to 77 patients with rheumatoid arthritis for six months. Results showed that patients treated with the hormone showed significant improvement after six months in articular index and pain score, and a decrease in ESR and morning stiffness.

Estrogens and Oxidative Stress

Estrogen is a cholanthrene ring composed of three 6-carbon rings (A, B, C) and one 5-carbon ring (D). Estrogen is a weak acid and can function as a proton donor or receptor. There is a body of evidence to suggest that estrogen has antioxidant properties. Some research suggests that estrogens may regulate oxidative process in some cells. However, there is also evidence suggesting that one of estrogen's metabolites, catecholestrogen, may be involved in free radical generation.

Endogenous sources of oxidative stress include inflammation, cytokines, and homocysteine. Exogenous sources include ultraviolet light, radiation, and environmental toxins. Exogenous defense against oxidative stress comes from dietary antioxidants, and endogenous defense mechanisms utilize enzymes and coenzymes inside human bodies.

If the body's defense mechanisms are working correctly, it should be able to cope with oxidative stress and homeostasis can be maintained. However, if for some reason homeostasis is not maintained, oxidative damage will result and physiological functions will become impaired, therefore increasing the risk and progression of age-related diseases.

In vitro studies conducted on estrogen and oxidative stress, have produced interesting results. A study by *Huh et al* found that the level of malondialdehyde (MDA), which is a marker of oxidative stress, is higher in the liver of the male rat than in the female rat liver. Thus suggesting that the female rat is subjected to lower levels of oxidative stress. This may be due to the female hormonal influence. Meanwhile, a study by *Miura et al* found that estradiol has the ability to inhibit lipid peroxidation. Back in 1993, *Mooradian et al* found that 17 beta-estradiol, 17 alpha-estradiol, and estriol reduced reactive oxygen specious accumulation in an *in vitro* study by 65%; however, estrone did not show any significant antioxidant properties. The authors concluded: "estrogens, especially estriol and 17 beta-estradiol, are naturally occurring antioxidants." In 1998 *Ayers et al* suggested that estradiol's apparent capability to protect against lipid peroxidation could be due to its ability to inhibit the generation of superoxide radicals and prevent further chain propagation.

Relevant *in vivo* studies include one by *Walsh et al* that examined the effect of estradiol on LDL flux in the carotid arteries of ovariectomized rats. The researchers concluded that their findings "support an antioxidant role for estradiol in the protection against LDL accumulation in the artery wall and subsequent progression of atherosclerosis." What about in humans? Myeloperoxidase (MPO) is an enzyme that consumes hydrogen peroxides and decreases ROS (reactive oxygen species) accumulation. It also plays a role in the termination of the whole process of free radical production in granulocytes by the inactivation of the NADPH-oxidase system. This enzyme is present inside granulocytes. *Bekesi et al* evaluated the activity and amount of MPO released at baseline and after some period of ET. Results showed that both increased significantly after treatment. The increased MPO activity and the NADPH-oxidase inactivation seemingly elicited by ET, might have further positive consequences since MPO has an effect on HDL-metabolism and the outflow of cholesterol from "foam cells", and NADPH-oxidase has a suspected role in LDL-oxidation and NADPH is one of the cofactors of NO-synthase (NOS). This Hungarian article did not specify the dose and treatment duration, however it did provide very interesting data that will hopefully be investigated further.

A number of oxidative stress markers are used in anti-aging clinics and laboratories. These molecules help scientists to determine the amount of free radical damage that is occurring in a cell, organ, or organism. The most commonly used markers include alkenals, hydroperoxides, 8-hyroxydeoxyguanosine (8-OHdG), and 8-Epi-prostaglandin F2a (8-epi-PG F2a) or isoprostane. Among these markers, 8-OHdG is

widely used in many anti-aging clinics and has a relatively credible index. It is the gold standard for measurement of oxidative damage to chromosomes and DNA. Its measurement reflects the amount of damage that has been caused to the entire body. Results of an unpublished study by *Kang et al.* investigating the effect of HRT on oxidative stress suggest that ET and human growth hormone therapy (hGHT) may help to reduce oxidative stress. Ten postmenopausal women were treated with ET or ET and hGHT for six months. For a control 48 women were not given any form of HRT. Results showed that 8-OHdG levels fell slightly in women receiving ET alone, and significantly in women receiving both ET and hGH treatment. From this pilot result it can be speculated that a possible mechanism for the anti-aging effect of HRT is the fact that it lowers oxidative DNA damage. Many experiments show that long-lived species have lower DNA damage than genetically similar species with a shorter lifespan. Therefore, suggesting that longevity is linked to low levels of DNA damage.

ALTERNATIVES TO ESTROGENS

What can be used instead of estrogens? There are a number of other treatments that can be used to combat the effects of menopause; these include black cohosh, ginseng (Korean), tibolone, and selective estrogen receptor modulators (SERMs) such as raloxifene, alendronate, calcitonin, and vitamin K_2.

Women complaining of hot flushes should first change their lifestyles. They should be educated to avoid dressing too heavily, drinking hot beverages or alcohol, and eating spicy food. They should also be educated on how to reduce stress and to breathe deeply when flushes are coming. Sleeping problems are considered to be secondary to hot flushes. Therefore, flush control can resolve these problems. They should be encouraged to try soy foods and black cohosh for more than a few weeks, and if this does not help the use of Effexor, Prozac, and Catapres should be considered.

For vaginal dryness, vaginal lubricants, estrogen creams or tablets, or plastic rings are effective. These agents seldom change the level of estrogen in the blood, therefore they are not effective with hot flushes and, of course, they do not have systemic side effects.

Treatment for the prevention of osteoporosis should be decided based upon the individual woman's bone density. If a woman's risk is not significant, she needs calcium, vitamin D, and exercise. If she has osteoporosis or is at high risk for osteoporosis, medications that help to increase bone mineral content should be prescribed.

As we know, menopausal women are at increased risk of developing heart disease. Therefore, serum cholesterol needs to be regularly measured and controlled. Recommended optimal cholesterol levels can be seen in Figure 10. Blood pressure and blood glucose levels also need to be kept under control. All of these goals can be achieved by adequate counseling, changes in lifestyle, and prescription of adequate medications.

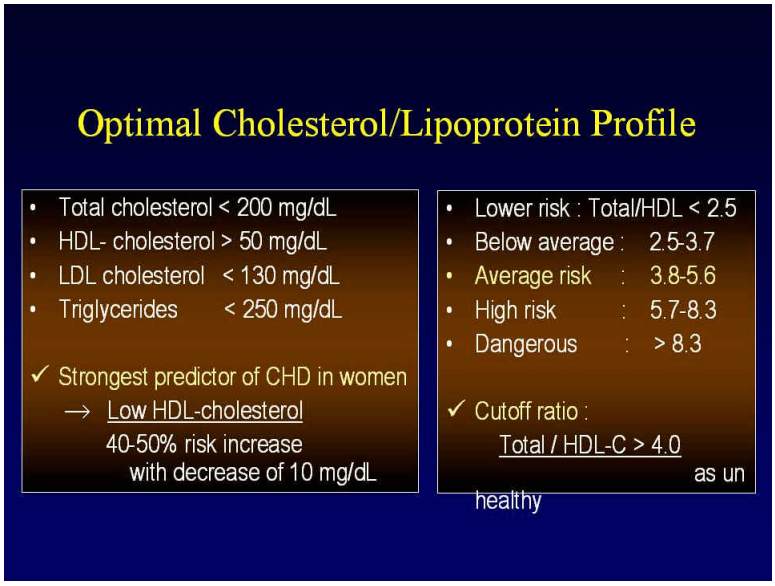

Figure 10. The optimal cholesterol/lipoprotein profile

Phytoestrogens are also known to benefit cardiovascular health. Interestingly, they also show an anti-neoplastic effect. In many pre-clinical and clinical studies, they have been shown to lower cholesterol and bone loss, and increase bone mineral density. Genistein, a phytoestrogen present in soy protein, has been found to improve endothelial dysfunction, which is a significant risk factor for heart disease.

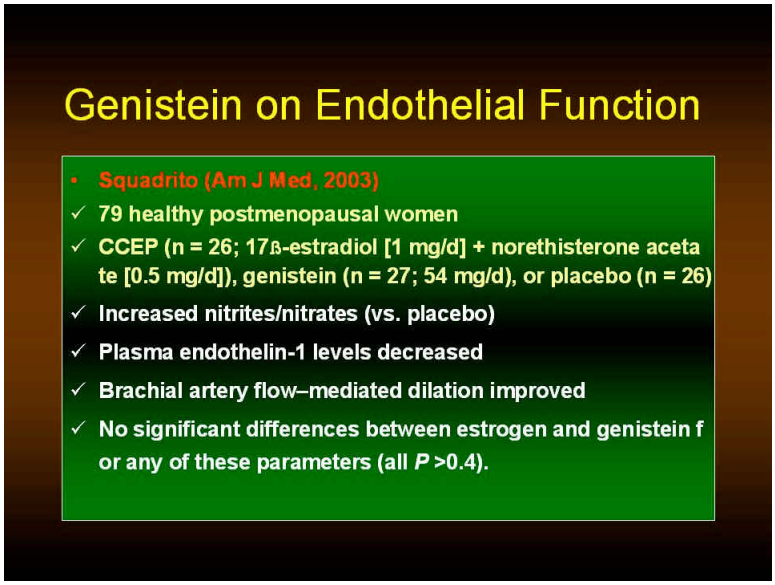

Figure 11. The effect of genistein on endothelial function.

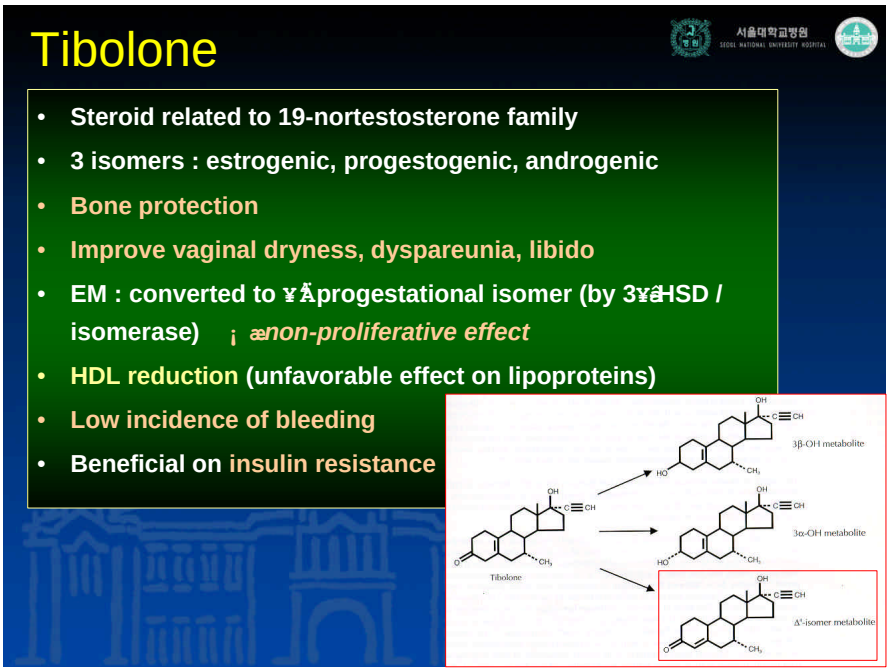

Figure 12. Benefits associated with use of the steroid tibolone.

Women who cannot be prescribed estrogen can be treated with tibolone (see Figure 12). If postmenopausal women complain of breast symptoms or experience a change in mammographic density, tibolone can be an alternative to estrogen. Selective estrogen receptor modulator (SERM) (see Figure 13) can also be considered as an alternative to ET.

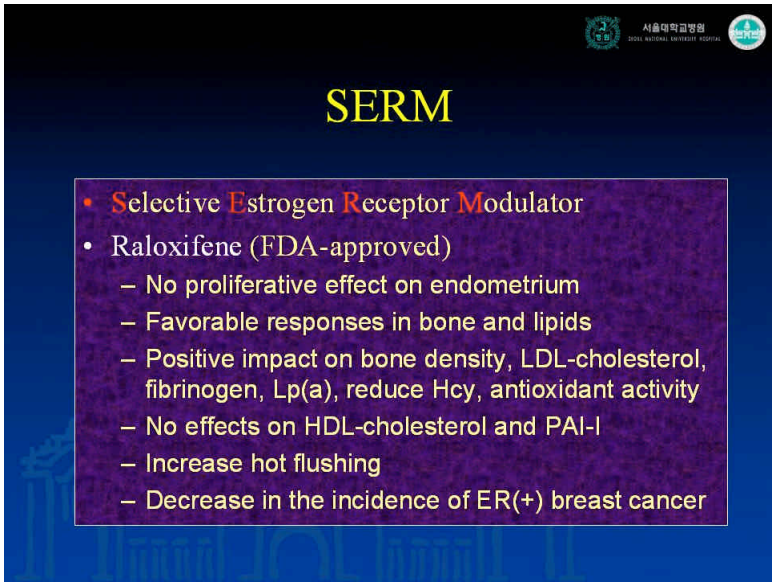

Figure 13. Benefits associated with Selective Estrogen Receptor Modulator (SERM).

CONCLUDING REMARKS

In conclusion, estrogen should be used cautiously after sufficient counseling and appropriate screening tests along with regular checkups. Alternative preparations, such as phytoestrogens, tibolone, SERM, or bisphosphonate should be considered for women with climacteric symptoms or established or

increased risk of osteoporosis.

Finally, all postmenopausal women should be encouraged to make certain lifestyle changes, these include stopping smoking, eating a nutritionally balanced diet, controlling body weight, taking adequate exercise, and stress reduction.

REFERENCES

Brussaard HE, Gevers Leuven JA, Frolich M, Kluft C, Krans HM. Short-term oestrogen replacement therapy improves insulin resistance, lipids and fibrinolysis in postmenopausal women with NIDDM. *Diabetologia*. 1997;40:843-849.

Chlebowski RT, Hendrix SL, Langer RD, *et al*. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA*. 2003;289:3243-3253.

Cutler RG, Mattson MP. Measuring oxidative stress and interpreting its clinical relevance for humans. In: Cutler RG, Rodriguez H, eds. *Critical reviews of oxidative stress and aging: Advances in basic science, diagnostics and intervention*. New Jersey: World Scientific; 2003:132-138, 1081-1086.

Hall GM, Daniels M, Huskisson EC, Spector TD. A randomised controlled trial of the effect of hormone replacement therapy on disease activity in postmenopausal rheumatoid arthritis. *Ann Rheum Dis*. 1994;53:112-116.

Harman D. Free radical theory of aging. In: Klatz R, Goldman R, eds. *The science of anti-aging medicine.* Chicago: American Academy of Anti-Aging Medicine; 1996: 15-31.

Lee JY, Choi YM, Ku SY. Effects of Continuous Combined HRT on Lipid Profile. In: Takeshi Aso, Takumi Yanaihara, eds, Seiichiro Fujimoto. *The Menopause at the Millennium*. New York: Parthenon Publishing Group; 2000:441-447.

Lee JY, Ku SY. Healthy aging in the new millennium. In: Schneider HPG, ed. *Menopause - The State of the Art*. New York: Parthenon Publishing Group; 2003:344-347.

The North American Menopause Society. Estrogen and Progestogen Use in Peri- and Postmenopausal Women: September 2003 position statement of The North American Menopause Society. Available at: http://www.menopause.org/HTpositionstatement.pdf.

The US Food and Drug Administration. Estrogen and Estrogen with Progestin Therapies for Postmenopausal Women. Available at http://www.fda.gov/cder/drug/infopage/estrogens_progestins/ default.htm. Date created: January 8, 2003; Date updated: March 2, 2004.

Wassertheil-Smoller S, Hendrix SL, Limacher M, *et al*. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA*. 2003;289:2673-2684.

Yoon BK, Kim DK, Kang Y, Kim JW, Shin MH, Na DL. Hormone replacement therapy in postmenopausal women with Alzheimer's disease: a randomized, prospective study. *Fertil Steril*. 2003;79:274-280.

ABOUT THE AUTHOR

Professor Ku received his Medical Degree in 1991 from Seoul National University (SNU) College of Medicine in Seoul, the top-ranked Medical School in South Korea. He has also received a Master's degree and PhD from SNU Postgraduate School, and continued his education with a fellowship in Reproductive Endocrinology and Infertility. He is currently working for SNU and SNU Hospital as Assistant Professor in the Department of OB/GYN, and has been qualified as NAMS Menopause Practitioner. He also serves as Korean representative of the A4M International Advisory Board and is Director of International Affairs to the Korean Academy of Anti-Aging Medicine (KA3M). He has published numerous articles both in Korea and internationally. He is the co-author of *Anti-Aging Medicine*, the first textbook of its kind in Korea and has been invited as Guest Speaker at A4M, AAWC, APAAC, AOFOG, KSMP meetings, etc. He has also published numerous medical and scientific articles in the field of reproductive endocrinology, both in Korea and internationally.