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**Hormone Replacement Therapy:
Implications of the Women's Health Initiative
for the Perimenopausal Singer**

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The larynx is sensitive to hormonal influences and changes within the body in both males and females. This is most apparent during puberty, when testosterone influences result in a lowering of the pitch of the voice in males, as a consequence of its effect on the musculature and the cartilages within the larynx. Estrogen and progesterone are the dominant sex hormones in women. The primary function of estrogen during the menstrual cycle is to build the uterine wall in preparation for ovulation and possible pregnancy; progesterone helps to stabilize this growth and stimulates the production of mucous in the uterus to aid in conception. The levels of estrogen and progesterone change throughout the menstrual cycle, and their effects can be seen in the larynx as the levels rise and fall.¹ Indeed, many women report a change in the voice during the premenstrual period that is characterized by vocal fatigue, decreased range, loss of power, and loss of certain vocal harmonics.¹ During the premenstrual period, levels of estrogen and progesterone are at their lowest in the menstrual cycle.

Menopausal women report similar symptoms of voice change, including vocal fatigue, decreased power, loss of the high range and loss of vocal quality.¹ The larynx changes with menopause. Because one of the chief functions of estrogen is in maintaining the tone and bulk of skeletal muscles, including those in the larynx, many women develop atrophy of the vocal fold muscles and a reduction in the thickness of the mucosa of the vocal fold with estrogen loss during menopause. This loss of muscle bulk of the vocal folds translates into increased vocal fatigue, decreased vocal intensity, changes in range, and changes in vocal agility. In some women, the cricoarytenoid joint loses some of

its mobility, which can also affect vocal agility.¹ Many women function well vocally without hormone replacement. However, approximately 20% of menopausal women will report some symptoms of menopausal vocal syndrome, for which hormone replacement therapy has shown to be of benefit.¹

In addition to the beneficial effects on menopausal vocal syndrome, hormone replacement therapy has been most beneficial in relieving the other symptoms of menopause, including hot flashes, emotional lability, atrophic vaginitis, sleep disorders, and osteoporosis. Hormone replacement therapy was also thought to decrease the risk of colorectal cancer, heart disease, and stroke; these were the reasons for advocating the general use of hormone replacement therapy in all postmenopausal women. The purpose of the Women's Health Initiative was to define the influence of hormone replacement therapy on these variables, as well as the relative risks of breast cancer, endometrial cancer, and death.² The results of the study were somewhat counterintuitive and have caused many women and physicians to abandon hormone replacement therapy because of fear of adverse effects. In this article, a review of the findings of the Women's Health Initiative will be presented as well as implications for professional singers who may have career advantages from using hormone replacement therapy in the menopausal years.

Design of the study

The purpose of the Women's Health Initiative was to examine the benefits and risks associated with the use of the most common hormone replacement

regimen used in the United States today.² The study included 16,608 women with an intact uterus who were postmenopausal. Half of the women were given placebo and the other half were given Prempro on a daily basis. Prempro is a preparation of low dose estrogen and medroxyprogesterone (a form of progesterone). The women were followed for an average of 5.2 years with physical examination and other testing. Once every 6 months, the study results were evaluated for any significant advantages or disadvantages of using Prempro that would warrant alerting the study participants so that they could make an informed decision about continuation or discontinuation of their medication or placebo. The study began in 1997 and was scheduled to end in 2005. The study was discontinued in July 2002 because the data showed increased risks in those taking Prempro that could potentially outweigh the benefits of the medication.

Results of the Study

The authors of the study assessed the risks and benefits of taking Prempro in categories of disease that are thought to be influenced by estrogen. It has long been believed that men have heart attacks and strokes at earlier ages than women because estrogen has a protective effect on cholesterol levels and presumably then on the blood vessels in the brain and heart.³ Thus, the incidence of heart disease and stroke were two main outcomes that were analyzed in the study. Estrogen alone, especially in high doses is known to predispose women to developing blood clots (deep venous thrombosis) in their

legs that can migrate to the lungs and obstruct blood flow there, a phenomenon called pulmonary embolism. Thus, the incidence of pulmonary embolism and deep venous thrombosis were factors that were investigated in this study, as well. Because estrogen is known to affect breast and uterine tissue, there have been numerous studies investigating the role of estrogen and estrogen replacement in the development of breast cancer and endometrial (uterine) cancer, and these were two of the variables studied in the Women's Health Initiative. The advantage of estrogen replacement in post-menopausal women is that it strengthens the bones and decreases the incidence of osteoporosis. Osteoporosis is a weakening of the calcium density of bones, which predisposes to fractures of long bones, the vertebrae, and the hip. Thus, the incidence of fractures, as measures of the incidence of osteoporosis, were other outcomes that were studied in this initiative.

Heart Disease

The study reported that of the 8506 women taking Prempro, 164 developed previously undiagnosed coronary heart disease during the study period. 122 of the 8102 women taking placebo developed coronary heart disease. This difference was statistically significant, indicating that although the risk of coronary heart disease is low in those taking placebo and in those taking Prempro, Prempro increased the risk of heart disease by 29%. Stated differently, under normal circumstances, 30 in 10,000 women per year will develop heart disease. If a woman is taking the combination of estrogen and

medroxyprogesterone, the risk of heart disease increases from 30 to 37 per 10,000 women per year; that is an additional 7 women in 10,000 each year will develop coronary heart disease. Although this risk was increased, the study found that the risk of death from coronary heart disease related events and the risk of needing surgery to repair vessels damaged from coronary heart disease was not significantly different in those taking Prempro versus those taking placebo.

Stroke

The risk of stroke was 41% higher in those taking the estrogen/medroxyprogesterone preparation than in those taking placebo, increasing from 21 per 10,000 women per year in the placebo group to 29 per 10,000 women per year in the group taking estrogen/medroxyprogesterone. Most of the increase in stroke in those taking Prempro was from nonfatal strokes.

Pulmonary Embolism and Deep Venous Thrombosis

The risks of pulmonary embolism and deep venous thrombosis in those taking the estrogen/medroxyprogesterone were both twice the risks seen in the placebo group. Deep venous thrombosis occurred at a rate of 13 per 10,000 women per year in the placebo group and 26 per 10,000 women per year in the Prempro group. Pulmonary embolism occurred at a rate of 8 per 10,000 women per year in the placebo group and 16 per 10,000 women per year in the estrogen/medroxyprogesterone group.

Breast Cancer

Newly diagnosed, invasive breast cancers had a rate of occurrence that was 26% higher in those taking estrogen/medroxyprogesterone than in those taking placebo. Among those taking the estrogen/medroxyprogesterone, the rate of breast cancer was 38 per 10,000 women per year. Among those taking placebo, the rate was 30 per 10,000 women per year.

Endometrial Cancer

The rate of endometrial cancer was not affected by hormone usage in this study, which is consistent with results of other studies that have shown that although estrogen alone increases the rate of endometrial cancer, the addition of a progesterone preparation with the estrogen decreases this risk.³

Colorectal Cancer

The rate of colorectal cancer was decreased by 37% in those taking the estrogen/progesterone pill (10 per 10,000 women per year) versus those taking placebo (16 per 10,000 women per year). Similar findings of a protective effect of hormone replacement therapy against colorectal cancer have been observed in other studies, however, the reasons for this protective effect are unclear.

Fractures

The overall rate of fractures was decreased by 24% in those taking the estrogen/progesterone combination in comparison to those taking placebo. The rate of hip fractures was 10 per 10,000 women per year, the rate of vertebral fractures was 9 per 10,000 women per year, and the rate of other osteoporotic fractures was 131 per 10,000 women per year in those taking Prempro. In those

taking the placebo, the corresponding rates were 15 per 10,000 women per year for hip fractures, 15 per 10,000 women per year for vertebral fractures, and 170 per 10,000 women per year for other osteoporotic fractures.

Who Should Use Hormone Replacement?

In interpreting the results of this study, there are several factors that one must take into consideration. The first, and probably most important, is the difference between clinical or “real life” significance and statistical significance. The results of this study indicate that in women taking estrogen plus medroxyprogesterone, one can expect 19 more adverse medical events per year per 10,000 women; that is, the rate of adverse events is increased by 15% (global indices of 170 versus 151 total events per 10,000 women per year). This rate includes the positive effects of estrogen/medroxyprogesterone on the rate of fractures and colorectal cancer. Thus, these numbers imply that the risks associated with taking the estrogen/medroxyprogesterone combination outweigh the benefits, from a statistical perspective. Thus, from the standpoint of global recommendations to all women, one cannot advocate the “blanket” use of combination hormone replacement therapy to all postmenopausal women, because doing so would put some women at risk for adverse events who otherwise likely would not suffer these consequences. And, it is now evident that hormone replacement therapy does not protect against coronary heart disease,

as was previously believed. So, use of hormone replacement therapy to protect against coronary heart disease cannot be advocated, either.

On the other hand, there clearly is some benefit to hormone replacement therapy for some women. Hormone replacement therapy does relieve the symptoms of menopause and it does decrease the occurrence of osteoporosis in those that are prone to developing it. There are other agents available to treat and prevent osteoporosis, including bone-enhancing agents such as calcitonin, etidronate, alendronate, and bisphosphonates. Symptoms of vaginal dryness that interferes with intercourse can be treated with a water-soluble lubricants such as KY jelly.

For symptoms of hot flashes, decreased libido, and orgasmic dysfunction, androgens appear to be beneficial and are recommended by some physicians. However, caution should be exercised in using androgens, as they are male sex hormones that can cause a deepening or lowering of the voice in females and can produce other masculinizing side effects. For the professional voice user, these effects can affect vocal performance and are counter-productive, especially if one of the target symptoms for treatment is a voice change. Thus, the professional voice user with menopausal vocal syndrome or with hot flashes, decreased libido, or orgasmic dysfunction may consider hormone replacement therapy, and should discuss this, as well as the risks as they pertain to her as an individual, with her physician. Women who are healthy and have no risk factors for stroke, heart disease, vascular disease, or breast cancer may consider hormone replacement therapy, understanding the increased risks associated with

the replacement. Women who have a family history of stroke, heart disease, vascular disease, and breast cancer and those who have a history of these illnesses themselves, probably should not take hormone replacement therapy because genetically, these women are already at increased risk for these events, and the addition of another risk factor may increase this risk.

One should be cautious using “herbal” preparations from soy or other plant extracts as alternatives to hormone replacement therapy, as these are merely estrogens in different forms. The dosages of estrogen in these preparations are not regulated, and the safety has not been tested by the Federal Drug Administration (FDA). It is possible for one to ingest greater amounts of estrogen from these ‘herbal’ preparations than from a prescription formulation that is tightly controlled by the FDA. Thus, if the goal is to minimize risk by not taking hormone replacement, then the use of over-the-counter herbal supplements made from plants that produce estrogens is not recommended.

Conclusion

The results of the Women’s Health Initiative indicate that the combination of estrogen/medroxyprogesterone as a form of hormone replacement in postmenopausal women offers a protective effect against osteoporotic bone fractures and colorectal cancer and increases the risk of coronary heart disease, stroke, venous thromboembolism, and breast cancer.² Menopausal vocal syndrome requiring treatment occurs in approximately 1 in 5 postmenopausal women.¹ Many women also experience other symptoms of menopause that are

bothersome enough to require treatment, as well. Hormone replacement therapy is an effective treatment for all of the symptoms of menopause, but has significant risks. Whenever possible, forms of treatment for symptoms of menopause other than hormone replacement therapy should be sought. However, the female professional voice user should be cautioned against using androgens because of their masculinizing effects on the voice. For the professional voice user whose vocal career is suffering from the effects of menopausal vocal syndrome and who wishes to continue her career, consultation should be sought from a physician to determine her individual risks associated with taking hormone replacement. The decision to begin or continue hormone replacement therapy should be made with the physician, balancing the risks with the possible benefits.

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