ESTROGEN REPLACEMENT THERAPY

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One of the most difficult decisions faced by women entering menopause is whether or not to take estrogen. Estrogen replacement therapy has obvious benefits, such as relief of hot flashes, depression, and vaginal atrophy. Estrogen has also been clearly shown to slow the rate of postmenopausal bone loss and to reduce the incidence of osteoporotic fractures by about 50%. However, there are also definite risks and side effects associated with taking estrogen. The discussion in this chapter is designed to help you understand the risks and benefits of estrogen replacement therapy, in order to help you make a more informed decision.

The fact that osteoporosis is far more common in women than in men and that bone loss accelerates after menopause suggests that an age-related decline in female sex hormones plays an important role in the development of osteoporosis. This concept is supported by the observation that women whose ovaries have been surgically removed lose bone at an unusually rapid rate for about four to six years following the operation. In women with intact ovaries, the amount of estrogen and other hormones secreted by the ovaries begins to decline around the time of menopause. The adrenal glands compensate in part for this decline in ovarian function by secreting certain androgens (male hormones) into the bloodstream which are converted elsewhere in the body into estrogens. However, despite this contribution from the adrenal glands, the amount of estrogen in the body falls at menopause.

SYMPTOMS OF MENOPAUSE

Menopause occurs around 50 to 52 years of age. At that time, the reduced estrogen secretion is no longer sufficient to produce menstrual cycles. In most women, during the first several years after menopause the amount of estrogen produced from adrenal sources is sufficient to support normal structure and the function of secondary sex tissues, such as the breasts, urethra, vagina, and vulva. With increasing age, however, as secretion of adrenal estrogen precursors declines these estrogen-dependent tissues begin to atrophy. The progressive reduction in estrogen levels leads first to a loss of ovulation and menstruation, followed by vaginal and vulvar tissue contraction, and finally, atrophy of all estrogen-dependent tissues. This prolonged period of progressive decline in estrogen levels, from age 40 to 70 and beyond, is called the *female climacteric*. The single point at which menstruation ceases is known as menopause.

The most common symptoms associated with menopause are hot flashes, those uncomfortable sensations of intense body heat accompanied by flushing of the skin on the head, neck, and chest and sometimes profuse perspiration. These symptoms may last anywhere from a few seconds to several minutes. In some women they occur only occasionally, while others are plagued with hot flashes several times every hour. For most women, hot flashes last about 1 to 2 years; however, in about 25% of women they may last as long as 5 years. In most cases, treatment with low doses of estrogen successfully relieves these symptoms.

As estrogen deficiency becomes more severe, atrophy of the vaginal mucous membranes may occur, resulting in vaginal itching or inflammation, pain on intercourse, and narrowing of the vaginal opening. Thinning or inflammation of the urethra (the urinary tract opening) may also occur and may cause pain on urination, frequent urination, or a tendency to leakage of urine. Estrogen replacement therapy, either orally or by direct application to the atrophied tissues, is nearly always successful in reversing these symptoms.

ESTROGEN PREVENTS OSTEOPOROSIS

One of the main reasons doctors recommend estrogen replacement therapy is that it prevents osteoporosis. It is now well established that estrogen replacement therapy reduces the incidence of osteoporotic fractures by approximately 50%. Estrogen works by preventing the increase in bone resorption that occurs at menopause. In contrast, estrogen has no effect on bone formation. Thus, estrogen therapy does not reverse established osteoporosis. However, if estrogen therapy is discontinued, bone loss resumes, possibly at an accelerated rate. Therefore, for estrogen therapy to be successful in the prevention of osteoporosis it must be started early, before significant bone loss has occurred, and continued indefinitely.

ESTROGEN, ATHEROSCLEROSIS AND HEART DISEASE

Estrogen may prevent atherosclerosis (hardening of the arteries). Estrogen therapy raises serum levels of HDL cholesterol, the "good cholesterol," which has been shown to protect against the development of cardiovascular disease. Recently, estrogen has also been shown to prevent the oxidation of cholesterol. An increasing body of research suggests that oxidized cholesterol, not cholesterol itself, is a primary cause of atherosclerosis. If estrogen can prevent the oxidation of cholesterol, it should also protect against the development of atherosclerosis.

Unfortunately, research on the effect of estrogen on heart disease is conflicting. Whereas some studies have shown that estrogen replacement therapy reduces the risk of heart disease by as much as 50 to 70%, other studies have shown a 50% increase in the risk of cardiovascular disease in women taking estrogen.

SIDE EFFECTS OF ESTROGEN

Women taking birth control pills have an increased risk of developing potentially dangerous blood clots, high blood pressure, and blood sugar abnormalities. It is thought that these side effects are due to the estrogen component of the pill. Since the dosage of estrogen in postmenopausal replacement therapy is lower than that found in birth control pills, these side effects have not been found to be a problem for postmenopausal women. However, both estrogen replacement therapy and birth control pills have been shown to increase the risk of gallbladder disease. Estrogen therapy could also conceivably worsen estrogen-dependent conditions such as uterine fibroids and endometriosis. Other side effects of estrogen include breast pain or worsening of fibrocystic breast disease, vaginal bleeding, high blood pressure, nausea, vomiting, headaches, jaundice, fluid retention, and impaired glucose tolerance.

ESTROGEN AND CANCER

Estrogen replacement therapy is known to increase the risk of endometrial (uterine) cancer. Studies show that women taking estrogen are between four and thirteen times more likely to develop cancer of the uterus than women who are not taking estrogen. Fortunately, the increased risk of endometrial cancer attributable to estrogen can be entirely eliminated if estrogen therapy is combined with a progestogen. However, progestogens themselves sometimes cause significant side effects, including dangerous blood clots, fluid retention, breast tenderness, jaundice, nausea, insomnia, and depression. In addition, most women who take a combination of estrogen and progestogen have a return of menstrual bleeding, which may require periodic biopsies of the uterine lining to screen for cancer.

Of greatest concern is the possibility that estrogen therapy could promote the growth of estrogen-sensitive breast cancers. In view of the fact that 1 in 9 women in this country will develop breast cancer, any increase in risk is a serious problem. An estimated 180,000 cases of breast cancer occurred in the United States in 1992, 32% of all female cancers.

At least 28 studies have looked at the relationship between estrogen replacement therapy and breast cancer. These studies have been reviewed by five different teams of investigators, using a statistical technique called meta-analysis. These analyses suggested that estrogen replacement therapy is associated with an increase in the risk of breast cancer, ranging from 1 to 30%.[1] In none of the studies was the increased risk statistically significant; in other words, these differences could have occurred by chance. However, because breast cancer is such a common problem, even a small increase in risk can have profound implications. For example, given a 1 in 9 (11.1%) chance of developing breast cancer, a 30% increase in risk (the highest number reported in the meta-analyses) would increase the overall breast cancer risk to 14.4%. If this worst-case scenario is accurate, then for every 1,000 women receiving estrogen replacement therapy, there would be 33 more cases of breast cancer (above and beyond the 111 already expected).

WHO SHOULD RECEIVE ESTROGEN?

Thus, despite certain clear benefits of estrogen replacement therapy, there is still considerable uncertainty among doctors about who should receive estrogen and for how long. Although the benefits are obvious, so are the risks. An estimated 30% of postmenopausal women do not lose significant amounts of bone. If these women do not have menopausal symptoms, then there is little reason for them to subject themselves to the risks of estrogen therapy. Unfortunately, it is not possible to predict accurately who will develop osteoporosis. However, periodic monitoring of bone mass using dual photon absorptiometry or CT scanning is useful for identifying established osteoporosis or for detecting those women who are losing bone at a rapid rate. Some women have chosen to hold off on taking estrogen until these tests demonstrate the need for it.

TYPES OF ESTROGEN MEDICATION

The most commonly used form of estrogen is known as *conjugated estrogens*, such as Premarin. Conjugated estrogens are not themselves physiologically active, but are converted within the body into active compounds. The physiologically active form of estrogen, 17 β-estradiol, is not well absorbed when taken by mouth. The small amount that does get absorbed is largely destroyed by the liver before entering the bloodstream. However, 17 β-estradiol is well absorbed through the skin and is the form of estrogen used in the newer estrogen patches. Estrogen patches are preferable to conjugated estrogens because they deliver the natural form of estrogen directly into the bloodstream in a slow, sustained manner. In that respect, estrogen patches resemble natural estrogen secretions more closely than do conjugated estrogens. Application of a single patch maintains a relatively constant serum level of 17 β-estradiol for approximately 3.5 days; therefore, the patches must be changed twice a week. The patch has been found to be clinically effective, in terms of relieving menopausal symptoms and maintaining bone density.

Estrogen is also available as a vaginal cream. At one time it was thought that estrogen cream could be used to relieve local symptoms, such as vaginal dryness and atrophy, without being absorbed into the system. However, it is now known that estrogen is well absorbed through the vaginal tissue into the blood and can cause the same side effects as orally administered estrogen.

With the various types of estrogens and the different patterns of dosing, with or without the use of progestogens, there are numerous possible regimens that can be prescribed for estrogen replacement therapy. No single pattern has gained wide acceptance. In fact, in a survey of 283 gynecologists in the Los Angeles area, fully 84 different patterns of estrogen replacement therapy were being employed. The main patterns were

1. cyclic estrogen alone
2. continuous estrogen alone
3. cyclic estrogen plus cyclic progestogen
4. continuous estrogen plus cyclic progestogen
5. continuous estrogen plus continuous progestogen
6. progestogen alone (cyclic or continuous)[2]

REDUCING CANCER *RISK WITH ESTRIOL*

As mentioned previously, the greatest concern about estrogen therapy is that it might cause cancer. Whether or not this concern is well founded (and we do not yet know, for sure), some women will not take estrogen and some doctors will not prescribe it, because of their fear of promoting cancer. Fortunately, there is a way to take estrogen that does not appear to increase the risk of cancer. In fact, this "alternative" method of estrogen replacement therapy could actually prevent cancer. Sadly, most physicians are unaware that there is another way to administer estrogen that is apparently as effective as, and probably safer than, the standard approach.

When doctors talk about estrogen, they usually forget that estrogen is not a single substance. On the contrary, estrogen exists in the body in at least three forms. The first two forms, *estrone* (abbreviated E1) and *estradiol* (abbreviated E2) are relatively potent estrogens, in terms of their ability to relieve hot flashes and other menopausal symptoms. Unfortunately, E1 and E2 also appear to be the forms of estrogen that promote cancer. The estrogen preparations usually prescribed for women

contain E1 and/or E2 or other related compounds that are converted in the body into E1 or E2. However, a third form of estrogen, known as *estriol*, also occurs naturally in the body. And, in contrast to the cancer-promoting effects of the other two estrogenic compounds, estriol has actually been shown to have anticancer activity.

Estriol is considered a weak estrogen because more estriol is required, compared to standard estrogen medications, to relieve menopausal symptoms. However, if an appropriate dose of estriol is given, these symptoms often do improve. A dose of 2 to 4 mg of estriol is considered equivalent to, and as effective as, 0.6 to 1.25 mg of conjugated estrogens or estrone.[3]

ESTRIOL AND ENDOMETRIAL HYPERPLASIA

The standard estrogen preparations frequently cause a potentially precancerous proliferation of the uterine lining, known as *endometrial hyperplasia*. In contrast, most investigators have found that estriol does not cause endometrial hyperplasia, even when given in doses as high as 8 mg/day. In one study, for example, 52 women with severe menopausal symptoms were given estriol continuously for six months in doses of 2 to 8 mg/day. Improvements in symptoms occurred within one month and persisted as long as estriol therapy was continued. The degree of symptom improvement was related to the dose – moderate at 2 mg/day, but marked at a dose of 8 mg/day. Estriol therapy also produced an improvement in vaginal atrophy and in the quality of the cervical mucus. However, endometrial biopsies failed to show hyperplasia in any case, regardless of the dosage of estriol used. Breakthrough bleeding also was not a problem.[4]

These observations suggest that estriol may be an appropriate choice where estrogen therapy is concerned. When judged in terms of endometrial proliferation, one of the unwanted effects of estrogen therapy, estriol is a weak estrogen. By other criteria, however, such as improvement in hot flashes and vaginal atrophy, estriol is a more potent estrogen.[5] Thus estriol therapy may produce some of the beneficial effects of estrogen therapy, while avoiding the undesirable side effects. In one report, large doses of estriol did cause some proliferation of endometrial tissue. However, the women given estriol in that study were also receiving a progestogen (such as Provera).[6] So far, no one has reported that administration of estriol by itself causes endometrial hyperplasia.

ESTRIOL AND BREAST CANCER

The other area of major concern with regard to estrogen therapy is in relation to breast cancer. Although the many studies on this issue have yielded no clear proof that estrogen promotes breast cancer, neither could these studies rule out the possibility that estrogen increases cancer risk by as much as 30%. Because that chance exists, safer forms of estrogen therapy are badly needed. Here, again, estriol may be an ideal choice.

More than 25 years ago, it was shown that estriol was not only noncarcinogenic, but that it inhibited the breast cancer-promoting effect of estradiol in mice.[7] Estriol also inhibited the development of breast cancer in rats induced by two different chemical carcinogens.[8] Because of this anticancer effect of estriol in animals, Dr. H. M. Lemon investigated whether estriol has any relationship to breast cancer in humans. He developed a mathematical formula, which he called the *estrogen quotient*, a measure of the ratio of the cancer-inhibiting estrogen (estriol) to the cancer promoting estrogens (estrone plus estradiol). If the estrogen quotient was high, that meant there was a large amount of estriol relative to the others and that the risk of cancer would presumably be reduced. Conversely, if the estrogen quotient was low, that meant there was little estriol present, compared to the levels of the cancer-promoting estrogens. Women with a low estrogen quotient would, therefore, be expected to have a higher risk of cancer. Lemon collected 24-hour urine samples from both healthy women and those with breast cancer. He found that the median estrogen quotient in healthy women was 1.3 prior to menopause and 1.2 after menopause. Only 21% of these women had estrogen quotients below normal. In contrast, among twenty-six women with breast cancer who had not received hormonal therapy or recent surgery, the median estrogen quotients were 0.5 and 0.8, respectively, with 62% of the women having values below normal.[9] These results indicate that women with breast cancer have a low level of estriol relative to the other forms of estrogen.

Another study also suggested a relationship between estriol and breast cancer prevention. Seventeen women with fibrocystic breast disease were given vitamin E, 600 units/day, for two months. Women with this condition are thought to have an increased risk of developing breast cancer. Because vitamin E has been reported both to relieve fibrocystic breast disease in humans and to inhibit chemically induced breast cancer in rats,[10] the effect of vitamin E on estriol levels was measured. Vitamin E treatment produced an 18% increase in the ratio of estriol to estradiol.[11] This increase in the relative concentration of estriol after administration of vitamin E may explain in part the reported anticancer effects of this vitamin.

Because of the apparent safety of estriol, doctors began carefully testing it in women with breast cancer that had metastasized (spread to other areas of the body). The dosage of estriol ranged from 2.5 to 15 mg/day. The results of this preliminary study were remarkable: In fully 37% of those receiving estriol, there was either a remission or no further progression of the metastatic lesions. These results were far better than expected, considering the natural history of metastatic breast cancer.[12]

OTHER ADVANTAGES OF ESTRIOL

Estriol has several other possible advantages over the commonly used forms of estrogen. Because estriol produces very little endometrial proliferation, it rarely causes postmenopausal vaginal bleeding. One of the problems with conventional estrogen therapy is that it is sometimes difficult to distinguish normal hormone-induced bleeding from pathologic bleeding (such as that due to cancer). Consequently, many women on hormone replacement therapy are subjected to diagnostic D&Cs (dilatation and curettage) and sometimes even unnecessary hysterectomies. The use of estriol would probably reduce the need for these procedures. Estriol may also more effectively lower the risk of thromboembolism (blood clots in the veins or lungs) than other estrogens.[13]

THE FORGOTTEN ESTROGEN

Despite these encouraging studies with estriol, there has been little interest among physicians in the United States in this "other" estrogen. In contrast, estriol has been available in Europe for many years. In an

attempt to educate American doctors about this important substance, Dr. Alvin H. Follingstad, of Albuquerque, New Mexico, published an article in the *Journal of the American Medical Association*, titled, "Estriol, the forgotten estrogen?" [14] Follingstad concluded in that article that estriol should be given to women who need estrogen therapy but who are at high risk for developing cancer. Considering that 1 in 9 women in the United States is expected to develop breast cancer, a case can be made that nearly the entire population is at risk. The role of estriol in postmenopausal hormone replacement therapy should, therefore, be given a closer look.

But, fifteen years after Follingstad alerted American doctors about the "forgotten estrogen," estriol is still ignored by all but a small group of open-minded physicians in this country. Many doctors have never heard of estriol; others refuse to try it for no other reason than the fact that it is different. For many physicians in this country, the code of conformity is very powerful. Living under the constant threat of rejection by colleagues, scrutiny by medical disciplinary boards, malpractice lawsuits, and an unwritten law that they are supposed to know everything, doctors often find it easier to run with the pack than to risk being different – even if being different means practicing a superior brand of medicine.

CLINICAL USE OF ESTRIOL

Tri-estrogen

Fortunately, some doctors are not intimidated by institutionalized mediocrity. One physician who has been unwilling to relinquish the joy of thinking for himself is Jonathan V. Wright, M.D., of Kent, Washington. For more than fifteen years, Dr. Wright has been internationally recognized as a leading authority in nutritional medicine, although, in the spirit of humility and noncompetitiveness he prefers to think of himself as a "trailing authority." [15]

In the early 1980s, Dr. Wright began working with estriol as an alternative to the conventional estrogen medications. Eventually, he came to the conclusion that the optimal way to use estriol was not by itself, but in combination with the more commonly used estrogens. The reason was that, in some women, the amount of estriol required to relieve menopausal symptoms was as high as 10 to 15 mg/day. Studies had also suggested that as much as 12 mg/day of estriol was needed to prevent osteoporosis. [16] Unfortunately, some women could not tolerate those relatively large amounts of estriol. In some cases, they caused nausea severe enough to require a dosage reduction.

Dr. Wright therefore developed an estrogen formula designed to maximize the benefits of estrogen, while minimizing the risks. By measuring serum levels and urinary excretion of the three naturally occurring estrogens, he concluded that the most appropriate proportions for a combination pill would be 80% estriol, 10% estrone and 10% estradiol. Wright named his formula tri-estrogen. He found that 2.5 mg of tri-estrogen is usually effective for relieving menopausal symptoms such as hot flashes and vaginal atrophy, although some women need 5 mg/day. Wright generally administers tri-estrogen in a cyclical fashion, 25 days per month, adding natural progesterone for 12 days at the end of the cycle. With the 2.5 mg dose of tri-estrogen and a low dose of progesterone, he hardly ever encounters withdrawal bleeding, although it does sometimes occur if larger doses of tri-estrogen and progesterone are given. According to Wright, the 2.5 mg dose of tri-estrogen is therapeutically equivalent to 0.625 mg of conjugated estrogens (Premarin), whereas the 5 mg dose is equivalent to 1.25 mg conjugated estrogens.

OSTEOPOROSIS PREVENTION

Although this specific combination of estrogenic hormones has not been tested with respect to osteoporosis prevention, its beneficial effect on menopausal symptoms suggests that it would also be effective for osteoporosis. Tri-estrogen may therefore be an ideal estrogen preparation for women who need estrogen therapy, but in whom the usual forms of estrogen pose an unacceptable risk. In some cases, estriol alone, at doses of 2 to 8 mg/day, is effective for relief of symptoms. However, as mentioned, those doses of estriol may not prevent osteoporosis. The decision about which type of estrogen to use can, therefore, be rather complicated.

The decision is made more difficult when one takes into account the work of John Lee, M.D., described in Chapter 15. According to Lee, natural progesterone alone effectively reverses osteoporosis, and additional estrogen does not make the progesterone more effective. If Lee is correct, then estrogen is necessary only to relieve menopausal symptoms, not for osteoporosis prevention. Thus, in cases where estriol alone relieves symptoms, that would be the preferred treatment. However, if the dose of estriol required to relieve symptoms causes nausea, then tri-estrogen might be preferable.

The appropriate choice of estrogen should be evaluated on an individual basis. At this point, additional research is needed before we will know how best to balance estrogen therapy to maximize osteoporosis prevention, while minimizing cancer risk. However, it is encouraging to know that we have safer options than those currently being offered by the average doctor.

ESTROGENS IN FOOD

In many situations, the use of estrogen is medically inadvisable, while in other cases, a woman may simply choose not to accept the risks of therapy. Occasionally, however, the effects of estrogen can be mimicked by eating specific foods that contain compounds with estrogenic activity. These compounds, which include genistein, daidzein, and equol, are known as *phytoestrogens* (plant-derived estrogens). Soy products such as tofu, miso, aburage, atuage, koridofu, soybeans, and boiled beans contain large amounts of phytoestrogens. High intake of phytoestrogens may partly explain why hot flashes and other menopausal symptoms are so infrequent in Japanese women. [17] However, it is not known whether phytoestrogens will help prevent osteoporosis. Other foods that have been found to have estrogenic activity include cashew nuts, peanuts, oats, corn, wheat, apples, almonds, and alfalfa. [18,19] Ginseng also has estrogenic activity and some herbalists use it as an alternative to estrogen. Ginseng should be used with caution, however, as an overdose can cause high blood pressure, anxiety, and insomnia.

ADDING TESTOSTERONE

In some cases, adding the male hormone testosterone to an estrogen regimen may be more effective than estrogen alone. The normal ovary manufactures testosterone and continues to do so, even after menopause. However, women who have had their ovaries removed may exhibit signs of testosterone deficiency, including loss

of libido and breast tenderness. Women who have undergone natural menopause also occasionally develop testosterone deficiency, which can be diagnosed by measuring the level of testosterone in the blood. Testosterone-deficient women may also find that the usual menopausal symptoms do not respond to estrogen therapy. In these cases, treatment with Estratest, a medication that contains both estrogen and testosterone, may reverse these symptoms. Correction of testosterone deficiency may also have a beneficial effect against osteoporosis. In a two-year study, administration of Estratest markedly increased bone density.[20]

However, Estratest is not for all women. In most cases, the ovary continues to produce adequate amounts of testosterone, even after menopause. The adrenal gland is also an indirect source of testosterone, both before and after menopause. Giving testosterone to a woman who does not need it can cause problems such as excessive hair growth, acne, and a deepening of the voice. However women whose menopausal symptoms have failed to respond to estrogen therapy, particularly women whose ovaries have been removed, should consider a trial of Estratest. Your doctor may wish to measure your serum testosterone level to determine whether Estratest is appropriate for you.

CONCLUSION

Estrogen replacement therapy is of value in the treatment of menopausal symptoms and for prevention of osteoporosis. However, because there are risks associated with estrogen, the decision of whether or not to use it should be made on an individual basis, after a detailed discussion with your doctor. Using estriol as a component of your estrogen program may reduce the risk of cancer associated with treatment. In some cases, phytoestrogens derived from foods such as soy may relieve menopausal symptoms. However, it is not known whether phytoestrogens will prevent osteoporosis. In women with testosterone deficiency, addition of testosterone to an estrogen regimen may provide added protection against osteoporosis.

NOTES

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