Estriol, the Forgotten Estrogen?

THERE is a definite need for a safe estrogen supplement for women who are at risk of breast or endometrial carcinoma but who are denied such therapy because of recent evidence that exogenous estrogen can induce carcinoma in susceptible women. The role of supplemental estrogen in the induction of carcinoma is controversial, but the consensus is that high risk contraindicates its use.1

Risk Factors

Who are the women considered to be at risk? A list of risk factors in approximate descending order of importance would be as follows: (1) previous carcinoma of breast or endometrium, with apparent long-term “euros” or better stated, “arrests,” (2) designated precancerous lesions combined with a strong family history of carcinoma of the breast, (3) breast-biopsy findings of a precancerous lesion such as ductal proliferation and cellular atypia, (4) mammography findings of increased density and asymmetrical density, prominent ductal pattern, diffuse punctate calcifications, and other patterns grouped under the term “dysplasia” and coupled with a positive family history, (5) a strong family history of breast cancer such as a mother and sister increasing the predicted incidence as much as fourfold, (6) severe fibrocystic disease of the breast, (7) late parity, and (8) early menarche and late menopause.

Need for Supplements

Who are the unfortunate women who desperately need estrogen supplements but are denied their use? The following conditions suggest the need for such supplements: (1) Most authorities on the subject of severe osteoporosis agree that estrogen supplements are a necessary part of the treatment in addition to supplements of calcium and vitamin D and increased ambulation.2 Halberstam,3 in a recent editorial, stated that “cancer of the endometrium is by no means a fatal disease and osteoporosis can be.” Of the estimated 4.2 million women in the United States with severe osteoporosis, 700,000 per year will suffer fractures leading to disability, deterioration, and in a substantial number, death. He believes that the risks of osteoporosis far outweigh the risk of endometrial cancer. (2) Women at risk with severe menopausal symptoms are denied estrogen. (3) Young oophorectomized women are denied estrogen for the same reasons. (4) Women with treated breast or endometrial cancer and long-term arrest who suffer severe estrogen deprivation symptoms are also denied treatment using estrogen. Treated breast cancer now is an absolute contraindication for estrogen treatment.

Before going any further, it is understood that endometrial cancer is by no means the problem in frequency and mortality that is breast cancer. If diagnosed early, it is relatively easy to treat and carries a respectable cure rate. Breast cancer, on the other hand, is the leading cause of cancer death in women in the United States. Cancer of the breast will develop in one of every 15 women. Approximately 90,000 new cases are diagnosed annually, and 37,000 women per year will die of it.4 Consequently the main thrust of this article will be directed to breast cancer.

Three Active Estrogens

Where does estriol fit into this problem? To understand estriol, a basic knowledge of all three active estrogens is needed. These are estrone, estradiol, and estriol, which are designated in endocrinologic terminology as E1, E2, and E3, respectively. Estradiol, or E2, is the prime or true ovarian estrogen secreted by the ovary but is also found in the complex interacting biosynthesis of the body. Estrone, E1, is an estrogen converted from androstenedione or estradiol by biosynthesis. Androstenedione is formed in the ovary but largely and more importantly, by the adrenal cortex. Estriol, E3, although a small amount may be secreted by the ovary, is a converted estrogen. It is mainly converted in the liver from estrone and also by a more circuitous route from estradiol. As has been known for many years, huge amounts are secreted by the placenta, and the urinary assay of estriol in the pregnant woman has been used as an index of the viability of the fetus—falling levels indicate fetal morbidity. Anyone more interested in the biosynthesis of these steroids than this simplistic explanation is referred to references 5 and 6.

Estrone has been thought, but certainly not clinically proved, to be more carcinogenic than the more natural estradiol. The recent furor over the role of conjugated estrogens in the induction of endometrial carcinoma indicated estrone as its principal component. All present commercial and popular orally administered estrogens are estrone, combinations of estrone and estradiol, or estradiol alone. Moreover, it has been shown that orally administered estradiol, including the micronized form, is mainly converted to estrone in the small bowel, thus making all the usual orally administered estrogens, in effect, estrone.7 Diethylstilbestrol, now used mainly for the hormone manipulation of advanced breast cancer, is not a steroid but is a chemical complex that acts like estrogen and is as carcinogenic as estrone.
Parenterally administered estradiol, however, retains its identity. This should be considered when an intramuscular combination of estradiol and testosterone is chosen for a lesser carcinogenic effect.

It has been well known and observed by clinicians that many oophorectomized and late menopausal women secrete a substantial amount of estrogen, and some show a surprisingly high level. This hormone is estrone converted from adrenal androstenedione peripherally (subcutaneous fat) and also in some organs. Hormone assays in these women show estrone to be the principal estrogen, with some estradiol and minute amounts of estriol. In relation to the incidence of breast cancer in these older women not receiving estrogen therapy and the role of oral estrogen supplements in other women, theoretically at least, estrone might be labeled the villain.

Now let us look at the third and neglected estrogen, estriol. In our country it has been labeled as a weak or ineffective estrogen and difficult if not impossible to obtain. Actually it is not weak if given in adequate doses. A dose of 2 to 4 mg is the equivalent of 0.6 to 1.25 mg of conjugated estrogen or estrone and is just as effective. It has been available in Europe for many years and is cited in articles on the equivalent doses of various estrogens. Importantly, estriol does not lose its unique identity when given orally as does estradiol. It remains estriol.

There has been a growing suspicion if not a conviction that estriol may not only be noncarcinogenic but indeed anticarcinogenic. Studies of ethnic groups with low incidence of breast cancer compared with the high incidence in our country and in Britain have shown higher urinary excretion of estriol in the low-incidence countries. Animal studies have shown that a high endogenous estriol level protects against the tumor-producing effects of estrone and estradiol. A recent study shows high urinary levels of estriol related to early first-child birth and low incidence of breast cancer.

Lemon, reporting on chemically induced rat mammary carcinoma, demonstrated a notable inhibition of mammary carcinogens with estriol therapy compared with therapy using estrone and estradiol. According to an unpublished study by Henry M. Lemon, John F. Foley, and M. Anne Kessinger, 5 mg and occasionally 15 mg of estriol, equivalent to a little more than 0.65 and 1.25 mg of conjugated estrogens was used, with the informed consent of patients, in postmenopausal women with breast carcinoma and metastases. This preliminary investigation was initiated as a trial of the safety and estrogenicity of the hormone in postmenopausal women with breast cancer and not primarily to test its activity as an alternative therapeutic estrogen for breast cancer. Thirty-seven percent receiving this small dosage had remission or arrest of metastatic lesions. They also suggested a long-term prospective study using estriol as a cancer preventive.

Conclusion

Do we indeed have a safer and possibly a noncarcinogenic estrogen that has been neglected, one that can be administered orally, maintains its unique identity, and is as effective as estrone or estradiol? There have been many articles written on this subject, most of which are animal or retrospective studies, but there has been a dearth of clinical studies. In a conversation with Helmut Vorherr, MD, from the University of New Mexico School of Medicine, the fact that there are some skeptical and critical research oncologists and endocrinologists who say we have as yet no positive proof of estriol as the waited-for safe estrogen, and that many of the articles do not meet the standards of critical scientific investigation was discussed. All the investigators, critical or noncritical, agree that clinical trials are urgently needed. Estriol, though readily available in Europe, is not available in the United States except for research projects and then with restrictions. This restriction is imposed by the Food and Drug Administration probably because like many other drugs in common use in Europe but not used here, estriol must first undergo a rigorous evaluation before being released.

According to conversations with R. Philip Eaton, MD, of the University of New Mexico School of Medicine, it is reported that protocols for clinical trials are now in progress—one of these in the Departments of Endocrinology and Obstetrics and Gynecology at the University of New Mexico School of Medicine. Do we as clinicians have to wait the years necessary for the completion of these trials before estriol becomes available to us? I think not. Enough presumptive and scientific evidence has been accumulated that we may say that orally administered estriol is safer than estrone or estradiol. The popular estrogens in use for many years can still be used for the low-risk patients, but when the high-risk patient who desperately needs estrogen for reasons already described comes to us, what shall we do? We can take the easy way out and say, "No estrogen for you." However, if our concern leads us to take a calculated risk, to stick out our necks and prescribe estrogens, let us have the estrogen that causes the least risk. Let us have the opportunity of doing our own clinical trials.

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Estriol was supplied by S. R. Kolli, PhD, of Carnrick Laboratories, Cedar Knolls, NJ.

References