PART 1 The Science Behind Bioidentical Hormone Replacement Therapy

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The use of bioidentical hormone replacement therapy (BHRT) is a patient-driven phenomenon that is gaining momentum. Driving this momentum is today's contemporary woman, who sees the years after 40 as a productive component of her life and career. She wants to continue to look and feel good and to be productive during and after menopause. Treatment-related side effects and the fear of an increased risk of cancer, both of which are associated with traditional hormone replacement therapy, are also prompting women to learn about other treatment options.

Women are reading about the benefits of BHRT (Table 1) in the popular press and are learning that it offers a more conservative yet effective approach to therapy. Empowered with the information that they no longer have to choose between unbearable menopause symptoms or the adverse side effects and risk of cancer that are associated with this traditional hormone therapy, many women are making informed decisions about their treatment for hormone deficiencies, and more and more are insisting on therapy with BHRT.

The purpose of this article is to provide a clear, concise definition of BHRT and then to review the scientific literature supporting the use of bioidentical hormones used to treat symptoms produced by natural or surgically induced menopause. This review will focus on the three estrogens endogenous in humans: estrone, estradiol, and estriol, as well as on progesterone and testosterone.

What Is BHRT?

“Natural hormone therapy” (NHRT) and BHRT are not synonymous. Although the term “natural” was originally used to refer to nonsynthetic substances and is still commonly used in the popular press, it has fallen into disfavor with health professionals because it refers to the source of a hormone rather than to its chemical structure (and thus its activity in the human body). For example, the term “natural” is often used to describe plant-based estrogens called phytoestrogens. However, phytoestrogens are not bioidentical to human hormones; they differ from and are much weaker in effect than endogenous human estrogens. “Bioidentical” refers to synthetic or nonsynthetic hormones that are identical in chemical structure (and thus in effect) to the hormones produced by the human body, regardless of their source.

Estradiol + Progesterone Therapy: The First Step in BHRT

A study by Hargrove et al1 examined the safety and efficacy of a once-daily dosage of micronized estradiol (0.7 to 1.05 mg) and progesterone (200 to 300 mg) combined in a single capsule that was administered in a continuous (as opposed to cyclic) manner to 10 menopausal women with moderate-to-severe vasomotor symptoms and/or vaginal atrophy. For comparison, five women in that study received Premarin 0.625 mg daily and Provera 10 mg daily for the first 10 days of each month. Serum estrone and estradiol concentrations increased significantly from baseline in both therapeutic groups and remained increased for the 12-month study period. The level of progesterone increased significantly in the subjects receiving estradiol and progesterone but remained unchanged in those receiving Provera. In that study, the combination of estradiol and progesterone resulted in an improvement of symptoms in all women with hot flashes and/or night sweats after 1 month of therapy and continued to provide relief during the 12-month study period. In contrast, three of the five women receiving Premarin and Provera continued to complain of hot flashes and one of the four who had experienced night sweats continued to report that symptom during the 12-month study period. Endometrial hyperplasia was uniformly prevented, and the hormone combination was well tolerated; there was a complete absence of withdrawal bleeding after 6 months of therapy. Only one patient discontinued treatment because of dizziness and sleepiness. In this landmark study by Hargrove et al,1 bioidentical hormones not only reproduced the clinical benefits of estrogens derived from the urine of pregnant mares and synthetic progestins but also produced better outcomes with fewer side effects.2-4 It could be argued that the most valuable contribution of Hargrove’s regimen is the improved patient compliance that usually results from such positive outcomes.

Tri-estrogen and Bi-estrogen: The Next Step

Wright4 introduced the move from estradiol as the sole estrogen used in BHRT to a triple-estrogen formula. The concentrations of each estrogen in his formula (estradiol, 80%; estradiol, 10%; and estrone, 10%) were first determined by his study of the serum estradiol levels in a group of premenopausal nonpregnant women. The result of that trial showed that in the patients studied, serum estradiol levels fluctuated less and were always significantly higher than the sum of the estrone and estradiol levels. By calculation, Wright determined that the average estradiol quotient ([estradiol/(estrone + estradiol)]) was 8.9. This indicated that the estradiol levels were nearly 10 times the concentration of estrone and estradiol.4 His research indicated that prescribing a combination of three bioidentical estro-

Table 1. Advantages of BHRT: A More Conservative Approach.

- Few or no side effects
- Decreased risk of breast cancer
- Improved compliance
- Synergistic osteoporosis protection
- Improved cardiovascular protection
gens found in triple-estrogen formulations would more closely mimic the natural proportions of endogenous hormones and would maximize the benefits of estrogen and minimize its risks.

Bi-estrogen (estradiol, 80% to 90% and estradiol 10% to 20%) is another popular estrogen combination. Double-estrogen therapy is based on the theory that because estradiol is 10 times more potent than estrone in controlling vasomotor symptoms, estrone is not needed for efficacy, and removing it from the formula may decrease the risk of breast cancer. Although estradiol is also associated with breast cancer, it is used in the double-estrogen formulation because of the lack of conclusive studies on the role of estril in the prevention of osteoporosis and cardiovascular disease. Also, estradiol is much more effective than estril in controlling the vasomotor symptoms of menopause, such as hot flashes and night sweats. Because double-estrogen and triple-estrogen formulations are less potent than conjugated equine estrogens (Premarin), the dosages of those bioidentical hormone combinations are higher (Table 2).

**The Case for Adding Estriol to a BHRT Regimen**

As mentioned previously, a major concern about estrogen therapy is an increased risk of breast cancer. Estriol and estradiol are relatively potent in providing relief of vasomotor symptoms such as hot flashes, but they are also associated with the development of cancer. Estriol is unique with respect to the other estrogens because it alone is not implicated in the etiology of human carcinoma. It is a weak, short-acting estrogen that, when administered in an indi- vided daily dosage, can also antagonize the effects of the stronger estrogens (estrone and estradiol). Although estriol is considered the weakest of the bioidentical estrogens, if the dosing is sufficient it can produce a full estrogenic effect on target tissue. This lends further justification for the use of the bi-estrogen formulation. The addition of estradiol results in a significantly lower dose requirement for estriol, the full estrogenic effect of which is then reduced.

Many studies have examined the relationship between oral estrogen replacement therapy and the development of breast cancer. It has been shown that estradiol and estriol and estradiol and estrone have revealed an increase in breast cancer risk from 1% to 30%. However, in many of those studies, oral conjugated equine estrogens (Premarin) were used. The only listed and known active ingredients of Premarin are estriol (an equine estrogen) and estrone. It has been established that estriol and estrogens that convert to estrone have harmful effects. Estriol, a metabolic end product that is excreted from the body, cannot be converted into estrone.

In 1966, Lemo et al demonstrated that reduced excretion of estriol is associated with an increased risk of breast cancer. They collected 24-hour urine samples from healthy women and those with breast cancer and found that the median estrogens quotient (EQ), a measure of the ratio of the cancer-inhibiting estrogen (estradiol) to the cancer-promoting estrogens (estrone + estradiol) for healthy women, was 1.3 before menopause and 1.2 after menopause. Only 21% of the healthy women studied demonstrated an EQ below normal. However, in the 26 women with breast cancer, the median EQs were between 0.5 and 0.8, and 62% of those women had an EQ value below normal. These results indicate that women with breast cancer have a low level of estriol in comparison with the levels of other estrogens. In addition, the study indicated that women without breast cancer have naturally higher estriol level compared with the levels of estrone and estradiol, which results in a higher daily EQ.

In another study, 17 women with fibrocystic breast disease were given 600 units of vitamin E for 2 months. Women with that condition are thought to have an increased risk of breast cancer. According to the results of this study, the treatment with vitamin E produced an 18% increase in the EQ.

In 1978, Follingstad presented the results of an unpublished study in which small doses of estriol (2.5 to 15 mg/day) were given to a group of postmenopausal women with metastatic breast cancer. In that group, it was reported that 37% of the women experienced a remission or arrest of their metastatic lesions. Estriol has been shown to be noncarcinogenic, and in mice it inhibited the carcinogenic effect of estradiol. Estriol also inhibited the development of breast cancer induced by two different carcinogenic chemicals in rats. Those beneficial effects of estriol and its very weak or negligible effect on the endometrium have justified the widespread use of estriol in Europe and elsewhere for the treatment of menopausal complaints in thousands of women.

**Estriol: Effect on Heart and Bones**

Results of research on the effect of estriol in maintaining bone density have been contradictory. Japanese studies have indicated the most promising results, perhaps because diets high in soy phytoestrogens may potentiate that effect of estriol. The effect of estriol on cardiovascular risk factors in postmenopausal women has not been clearly established, and more research is needed in that area as well. However, those shortcomings may be overcome by incorporating estriol into bi-estrogen or tri-estrogen formulations. No studies have evaluated the effects of such estrogen formulations on the prevention of osteoporosis or heart disease. However, an estriol level greater than 50 pg/ml is associated with the prevention of both those diseases and can be monitored.

**Estriol for the Management of Postmenopausal Symptoms**

Although most investigators have found that estriol at dosages of 2 to 8 mg given as a single daily dose does not cause endometrial hyperplasia, it can be effective in decreasing the symptoms of menopause, which include hot flashes, insomnia, and frequent urinary tract infections. In one study, 52 women with severe menopausal symptoms were given 2 to 8 mg/day of estriol continuously for 6 months. The degree of symptom improvement was related to the dosage given. Moderate improvement was noted at a

### Table 2. Estrogen Dosage Conversion Chart

<table>
<thead>
<tr>
<th>Premarin (mg)</th>
<th>Bi-estrogen and Tri-estrogen (mg)</th>
<th>Estriol (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>1.25</td>
<td>2.5</td>
</tr>
<tr>
<td>0.625</td>
<td>2.5</td>
<td>5.0</td>
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dosage of 2 mg/day, and marked improvement was noted at a dosage of 8 mg/day. A significant improvement in symptoms was noted within 1 month of the start of the study and persisted for the duration of estradiol therapy. Therapy with estradiol also reversed vaginal atrophy and improved the quality of cervical mucus. No breakthrough bleeding occurred in any of the subjects.

In a larger prospective study, 111 patients received estradiol succinate in a dosage of 2 to 12 mg/day for up to 5 years (M = 2.2) for menopausal management. Estradiol therapy was very effective in the treatment of climacteric complaints and genital atrophy. Hot flashes were completely eliminated in 71% of cases and became less frequent and less intense in 21% of the patients studied. Vulvar atrophy was completely eliminated in 44 of 61 patients and improved in 12. Of those 111 subjects, 22% required a daily dosage of 2 mg of estradiol, 70% required a dosage of 4 mg, 6% required 6 mg, and 2% required 8 mg to ameliorate climacteric symptoms. The author stated that “It is remarkable that estradiol does not proliferate the endometrium when given in one dose a day.”

In Europe, estradiol is used as a vaginal cream and has become the therapy of choice for postmenopausal vaginal atrophy. Luisi et al. found estradiol vaginal cream to be superior to Premarin vaginal cream in the treatment of vaginal atrophy. This conclusion was based on the undesirable effects of Premarin cream on the blood levels of estradiol and estrone and the subsequent increase in both the sex hormone-binding globulin level and the endometrium. The estradiol cream studied did not produce those changes. Luisi et al. also reported similar results by other researchers who compared the effect of estradiol vaginal cream with that of estradiol vaginal cream.

Estradiol offers a potential therapeutic option for the menopausal management of women at high risk of breast cancer or for those who are fearful of their risk of developing breast cancer. It may also be a good choice in women with fibrocystic breast disease, uterine fibroids, endometriosis, ovarian cysts, or any other condition that can be worsened by the stimulatory effects of the stronger estrogens. Because it appears to exert very little (if any) effect on blood clotting factors, it may also be an option for women at risk of deep venous thrombosis or thromboembolism. Bi-estrogen or tri-estrogen formulations may be the therapy of choice for women who require protection from cardiovascular disease or osteoporosis.

References