

## PART 3 The Science Behind Bioidentical Hormone Replacement Therapy

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### Breast Cancer Risk and Hormone Replacement Therapy

The association of breast cancer risk with unopposed estrogen therapy (ERT) or combined estrogen and progestin therapy (hormone replacement therapy [HRT]) remains controversial despite the publication of more than 50 epidemiologic studies during the last 25 years. The current prevailing opinion appears to be that "estrogen replacement therapy [ERT] modestly increases the risk of breast cancer, and HRT increases the risk more than ERT."<sup>1</sup> However, it should be pointed out that two of the recent studies<sup>2,3</sup> that support this opinion both mention that medroxyprogesterone acetate (MPA), a synthetic progestin, was used in the majority of the women studied. In Part 2 of this series,<sup>4</sup> it was clearly demonstrated that synthetic progestins and progesterone are completely different hormones. In the final segment of this article, additional evidence of the vast differences between synthetic progestins and bioidentical progesterone is again presented.

### Progesterone and Breast Cancer

Progesterone, like its synthetic "cousins" the progestins, protects against endometrial hyperplasia caused by ERT. However, the antiproliferative effect of progesterone differs from that of the synthetic progestins in that it is not limited to the endometrium. The protective action of progesterone on breast tissue was demonstrated in a study by Chang et al.<sup>5</sup> In that study, the effects of topically applied estradiol and/or progesterone on human breast milk-duct epithelial cells were tested in 40 premenopausal women. The subjects studied were divided into four groups: Those in group A applied placebo cream, group B applied estradiol cream (1.5 mg/day), group C applied progesterone cream (25 mg) daily, and group D applied both estradiol and progesterone daily. After 10 to 13 days of treatment, a sample of milk-duct tissue was removed during previously scheduled breast surgery. The effects of those hormones on the cell proliferation rates of these samples were as follows: Estradiol increased cell proliferation rates by 230%, but progesterone decreased that rate by more than 400%. When the combination of estradiol and progesterone was applied, the rate of milk-duct cell proliferation remained normal. These results provide clear evidence that unopposed estrogen stimulates the hyperproliferation of breast epithelial cells and that progesterone protects against that hyperproliferation.<sup>5</sup>

Foidart et al<sup>6</sup> expressed concern about the study by Chang et al<sup>5</sup> because the hospitalization and general anesthesia for breast surgery could have produced stress-induced disturbances in endogenous progesterone and the ovarian secretion of estradiol that could have interfered with effects of the applied hormones and thus the results

of the study. For this reason, Foidart et al<sup>6</sup> repeated the protocol in 40 postmenopausal women. The data from that double-blind, randomized trial strongly supported the observations by Chang et al,<sup>5</sup> who concluded that progesterone may produce a beneficial effect on estradiol-induced epithelial cell proliferation.

A prospective epidemiologic study<sup>7</sup> conducted at Johns Hopkins also demonstrated the protective role of progesterone against breast cancer. In that study, 1083 women who had been evaluated and treated for infertility were followed up for 13 to 33 years. These women were categorized according to the cause of infertility: endogenous progesterone deficiency or nonhormonal causes. Results of the study showed that the risk of breast cancer was 5.4 times greater in the subjects who had a low progesterone level when compared with subjects who had a normal progesterone level. This result was particularly striking because fewer women who had never given birth and fewer women with a late first birth (both of which are risk factors for breast cancer) were in the group with a low progesterone level. Women with progesterone deficiency also experienced a 10-fold increase in the death rate from all malignant neoplasms when compared with women who had a normal progesterone level.

In a third study,<sup>8</sup> the protective effect of progesterone or tamoxifen was investigated in estrogen-induced breast cancer in W/Fu rats. Results of that study indicated that the induction rate, multiplicity, and size of estrogen-induced mammary tumors were reduced by the simultaneous administration of either progesterone or tamoxifen. The study also demonstrated that the inhibitory effect of progesterone or tamoxifen in estrogen-induced carcinogenesis is attributable to interference with the binding of estrogen to the estrogen receptors on the target cells.

The studies cited above strongly suggest that with respect to breast cancer risk, progesterone offers a safer, more conservative approach to HRT. The results also indicate the reasons for which millions of women in the United States have opted for therapy with bioidentical hormones, which are not commercially available and must be compounded by specialty pharmacists, instead of conjugated equine estrogens and synthetic progestins.

### Progesterone and Estrogen Dominance: A Matter of Balance

An important concept in bioidentical hormone replacement (BHRT) is that of estrogen dominance (hyperestrogenism). This concept refers to a hormonal imbalance in women in which the level of progesterone does not balance the level of estrogen. Estrogen dominance can be caused by anovulatory cycles, luteal phase defect, adrenal exhaustion, ERT, HRT in which a synthetic progestin is used, oral contraceptives, or receiving no therapy during menopause. Hargrove and Osteen<sup>9</sup> demonstrate that 100 mg of progesterone given intramuscularly usually relieves (within a matter of hours) the symptoms of hyperestrogenism in a patient receiving estrogen replacement. Common symptoms of hyperestrogenism,

which can be relieved by balancing estrogen with bioidentical progesterone, are listed in Table 1.

In a cross-sectional survey,<sup>10</sup> the effect of progesterone on quality of life (QOL) was compared with that produced by MPA. The 176 female subjects had been receiving HRT with progesterone for 1 to 6 months at the time of the study, before which they had received HRT with MPA. Telephone interviews were used to assess QOL by means of the Greene Climacteric Scale and the Women's Health Questionnaire. Women using the progesterone-containing regimen reported a significant improvement in vasomotor symptoms, somatic complaints, and anxiety and depressive symptoms when compared with women treated with the MPA-containing regimen.

### Progesterone: Not Just for Endometrial Protection

A synthetic progestin or progesterone is usually prescribed only when needed to protect against endometrial cancer caused by ERT. Therefore, neither synthetic progestin nor progesterone is given to women who have undergone hysterectomy. This practice must be questioned, because after a complete hysterectomy, when the production of estrogen and progesterone is greatly reduced, only estrogen is typically prescribed for the patient. Table 2 lists several reasons for which every woman, regardless of whether she has an intact uterus, should receive bioidentical progesterone as part of treatment with ERT. A strong case could also be made for providing progesterone supplementation for women who use any form of birth control that prevents ovulation (eg, oral contraceptives), because no ovulation means no release of progesterone during the luteal phase. According to Prior et al,<sup>11</sup> premature osteoporosis can be caused by a lack or absence of progesterone during the luteal phase of the menstrual cycle; this may be especially important in teenage girls, whose bones are still developing.

### Progesterone and Vasomotor Symptoms

Leonetti et al<sup>12</sup> assigned 102 healthy women who were within 5 years of menopause to receive 20 mg/day of transdermal progesterone cream or placebo in a randomized, double-blind, placebo-controlled trial of control of the vasomotor symptoms of menopause. All subjects were free of hormonal therapy for at least 1 year before the initiation of the study. A review of the subjects' weekly diaries of symptoms chronicled an improvement in or resolution of vasomotor symptoms in 83% of those treated with transdermal progesterone cream and in 19% of those who had received placebo.

These results support the observations of Hargrove et al<sup>13</sup> regarding hot flashes in patients with a normal or elevated serum estradiol level. Those authors suggested that "hot flashes can occur at various circulating levels of estrogen and cannot be considered the sine qua

non of estrogen deficiency." From a clinical point of view, Hargrove et al state that perimenopausal women who are experiencing hot flashes are best treated with progesterone alone (100 mg orally TID on days 16 through 27 of the menstrual cycle) if they are continuing to menstruate. The authors explain that in such women, the level of estrogen is not yet low because a consistent serum level of at least 50 pg/mL of estradiol is necessary for menstruation to occur.<sup>13</sup> It has been my clinical experience that applying 0.5 mL of a 3% progesterone cream twice daily on days 16 through 25 of the menstrual cycle can be used to produce the same results.

### Testosterone: Not Just For Men

Despite data indicating the importance of androgens to libido and feelings of well-being in women from as far back as the early 1960s,<sup>14</sup> the traditional myth of testosterone as the "male hormone" has deprived many women of a valuable therapy. Today, many women are approaching their healthcare providers with questions about and requests for testosterone.

Testosterone replacement should be included in a comprehensive HRT program for women experiencing natural or surgically induced menopause because the androgen level of those women declines. The primary target populations are women with the symptoms of testosterone deficiency, surgical menopause, or premature ovarian failure and those receiving ERT.

Women who have undergone surgically induced menopause have traditionally been viewed as the most likely candidates for testosterone replacement because surgical removal of the ovaries leads to a precipitous decline in testosterone (approximately 50%)<sup>15</sup> as well as estrogen levels. In contrast, during perimenopause, the testosterone level slowly and gradually declines.<sup>14</sup>

Two recent studies<sup>16,17</sup> of 70 postmenopausal women who ranged in age from 46 to 55 years of age highlighted the importance of considering testosterone in another specific group of women: those receiving ERT. In the first study,<sup>16</sup> 46 of those 70 women used oral estrogen. The other subjects did not. The authors found that exogenous estrogen increases sex hormone-binding globulin, which in turn reduces free or bioavailable testosterone levels. The study results also showed that in women taking estrogen, the free testosterone level was reduced by 53%. In the second study by Casson et al,<sup>17</sup> the effect of 2 mg/day of estradiol in women experiencing natural menopause was examined. The study indicated that the level of sex hormone-binding globulin increased by 160% and the mean circulating level of total testosterone decreased 42%.

The complaints most prevalent in women in whom testosterone deficiency is suspected include a diminished sense of general well-being and decreased libido, as well as diminished sexual pleasure, a decrease in the perception of clitoral sensations, and markedly

**Table 1. Symptoms of Estrogen Dominance.<sup>13</sup>**

- |                   |                     |
|-------------------|---------------------|
| ■ Weight gain     | ■ Breast tenderness |
| ■ Fluid retention | ■ Mood swings       |
| ■ Headaches       | ■ Fatigue           |
| ■ Hot flashes     |                     |
| ■ Food cravings   |                     |

**Table 2. Rationale for the Use of Progesterone in All Women Receiving Estrogen Replacement Therapy.**

- To prevent symptoms of estrogen dominance
- To decrease the risk of breast cancer
- To reduce the risk of osteoporosis
- To improve cardiovascular benefits

diminished orgasms.<sup>15,18</sup> Loss of muscle tone and dry scalp, hair, or skin can also occur.<sup>15</sup>

A "working definition" of testosterone deficiency in women has been proposed.<sup>15</sup> That definition includes low libido, blunted or diminished motivation, persistent fatigue, a decreased sense of well being, sufficient plasma estrogen levels, and low circulating bioavailable testosterone (either a low total testosterone/sex hormone-binding globulin ratio or a low level of free testosterone in the lower third of the normal premenopausal range). Women who exhibit those symptoms but have a normal testosterone level may also benefit from testosterone supplementation. Laboratory values should not be the only criteria for such treatment.<sup>18</sup>

When bioidentical testosterone (testosterone USP) is administered to achieve physiologic rather than pharmacologic replacement levels, deleterious effects have not been reported.<sup>13</sup> When androgens are confirmed to be deficient by measurement, Hargrove et al<sup>13</sup> recommend 2.5 to 5 mg/day of orally administered micronized (bioidentical) testosterone. Another practitioner<sup>19</sup> experienced in the use of BHRT writes that doses of orally administered micronized (bioidentical) testosterone for women usually average 2 to 10 mg/day.

Rako<sup>18</sup> however, is a proponent of oral low-dose methyltestosterone (MT) 0.25 to 0.8 mg per day, which also does not produce virilizing side effects such as acne and an increase in downy facial hair. Rako points out that MT, unlike bioidentical testosterone, is not readily converted to estrogen; this is advantageous.<sup>20</sup> She mentions that women who initiate supplementation with oral MT may sometimes receive benefits such as increased energy and a greater sense of well-being without an improvement in the perception of genital sensation and an increase in libido. As a result, Rako recommends that a once-daily application of a small amount of topical testosterone, USP ointment (1% to 2%) be applied to the genital mucosa for the first few weeks of therapy. She explains that when local testosterone receptors are well supplied, sensation and libido return. She cautions against long-term daily use of topical testosterone on the genital mucosa because of the potential for overstimulation and gradual clitoral enlargement (both of which are reversible). For this reason, she recommends changing therapy to an oral testosterone supplement for maintenance after libido has improved and the capacity for genital stimulation has been established.<sup>18</sup>

It has been my clinical experience that therapy with testosterone is often ineffective in restoring libido if the patient exhibits estrogen dominance. When the imbalance in estrogen and progesterone is corrected, testosterone is effective in restoring libido.

Benefits of androgen therapy include not only improvement in libido but an increase in the sensitivity of the genitals (especially the clitoris) and a corresponding increase in sexual satisfaction.<sup>18</sup> Other benefits include an improved feeling of well-being, relief from vasomotor symptoms that are unresponsive to treatment with estrogen alone,<sup>14</sup> a higher energy level,<sup>14</sup> improved mood (reduced anxiety and depression),<sup>15</sup> positive effects on bone, and reduced triglyceride levels.<sup>14</sup>

## Route of Administration

Hormones are usually delivered orally, transdermally, or sublingually. Transdermal or sublingual routes are thought to be more

advantageous because they bypass first-pass hepatic metabolism, which is also the case when the hormones are endogenously produced. Further discussion of the advantages and disadvantages of the different routes of administering HRT is beyond the scope of this article. However, it is important to note that the oral bioavailability of progesterone is very low. More than 90% of orally administered progesterone is metabolized during first-pass metabolism through the liver, which causes an abrupt increase in progesterone metabolites to an unphysiologically high level.<sup>21</sup> The metabolites that are reduced at the 5- $\alpha$  position can cause sedation,<sup>21</sup> which can be clinically useful for menopausal women with insomnia. For those women, oral dosing at night may be preferred.

## Compliance: The #1 Problem

Despite a long list of established benefits, HRT has not achieved its anticipated role in preventive medicine.<sup>22</sup> Less than 8% of postmenopausal women choose to take HRT because they fear resultant cancer or side effects. In addition, those who initiate HRT often discontinue treatment prematurely, and long-term benefits are not achieved. At least 5 years of consecutive treatment is required to reap the beneficial effects of ERT.<sup>23,24</sup> Unwanted side effects such as bloating, breast tenderness, irregular bleeding, and weight gain are the most common reasons for the termination of HRT; those symptoms occur in 33% to 66% of women during the first 2 years of treatment.<sup>25</sup>

The ideal HRT regimen would satisfy the needs of all women. A greater sensitivity to the variation in needs of each patient would greatly improve compliance.<sup>26</sup> A practical way of accomplishing this would be to expand the paradigm from that of simply replacement to one of replacement *and* balancing. "Balancing" implies the adaptation and individualization of the hormone regimen to meet the specific needs of each patient. The greatest benefit of hormone balancing with bioidentical progesterone is the improved compliance that results from a decreased risk of breast cancer and fewer symptoms of hyperestrogenism. Such individualized dosing, which maximizes response and limits unwanted effects, is possible if bioidentical hormones are used and a compounding pharmacist formulates the exact dose needed in the best dosage form with the most effective route of delivery.

According to one source,<sup>13</sup> "Attempting to determine a reasonable HRT program based solely on the management of symptoms defies logic." Customization should be based not only on each patient's subjective clinical symptoms, which can be especially misleading in elderly women, but also on objective measurements such as serum or saliva hormone levels, cholesterol levels, and bone density measurements.<sup>13</sup>

Baseline saliva or serum hormone values should be recorded before hormone therapy is initiated. Initial dose-titration can be based on clinical symptoms. However, after climacteric symptoms have been controlled, the level of estradiol (at a minimum) should be rechecked to ensure the adequacy of treatment. It should not be assumed that disappearance of hot flashes means that the estrogen replacement is at an optimal level.<sup>13</sup>

## Conclusion

Not too long ago, the "gold standard" of insulin therapy was insulin derived from pigs. Today, that type of insulin is not available

because bioidentical human insulin, which is more effective, is used. The information presented in this article, while certainly not definitive, provides enough compelling evidence to suggest that the use of conjugated equine estrogens and synthetic progestins and estrogens is also outdated and that those hormones should no longer be administered. Today, bioidentical hormones are more effective and more safe for patients.

Compliance is the number one-problem with respect to HRT today; women fear that cancer or side effects might result from treatment. However, women are also educating themselves about how they can reduce those negative aspects of therapy by using bioidentical hormones. Practitioners can improve compliance by expanding their hormone therapy paradigm from simply replacement to replacement and balancing.

Because the use of bioidentical hormones in women is in its infancy, few clinical trials have been conducted on that topic. Until the results of such studies have been published, little valid information on the use of bioidentical hormones will be available. In the interim, it is hoped that this review will provide enough evidence to show that generalized conclusions about ERT and HRT that are based on studies in which conjugated equine estrogens and synthetic progestins were used do not necessarily apply to the results produced by bioidentical hormones. In fact, bioidentical hormones will probably provide better outcomes with fewer risks and side effects.

Millions of dollars are currently being spent on the 15-year Women's Health Initiative study, which is described by the National Heart Lung and Blood Institute as "one of the most definitive, far reaching clinical trials of women's health in America."<sup>27,28</sup> Unfortunately, the effects of conjugated equine estrogens (Premarin) and the synthetic progestin MPA (Provera) are the focus of that study. It is my hope that similar research will soon be conducted to clarify the more promising effects of BHRT.

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