Hormones in Wellness and Disease Prevention: Common Practices, Current State of the Evidence, and Questions for the Future

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KEYWORDS

• Hormones • Estrogen • Progesterone • Testosterone
• Thyroid • Growth hormone • Wellness • Prevention

The study and use of hormones have long been the domains of endocrinology, which is primarily focused on the pathologic phenomena encountered in the human body as they relate to hormones. No specific field in medicine has been designated to study and analyze the effects of hormones on wellness and disease prevention. As the field of wellness and disease prevention expands rapidly, it behooves the primary care practitioner, the first physician contact between the patient and the health care system, to become conversant and comfortable with hormone treatments as they relate to wellness and disease prevention.

Extensive scientific literature addresses the crucial role hormones play in the physiologic processes that maintain homeostasis. Much controversy surrounds the clinical use of various hormone therapies to support and maintain these processes in the aging patient. This article attempts to clarify some of the confusion and controversy surrounding estrogen, progesterone, testosterone, growth hormone, and thyroid hormones and discuss their roles as supported by the present state of evidence in disease prevention and aging as they apply to the primary care practice.

Hormones represent specific proteins produced by the human endocrine organs: pituitary, adrenals, thyroid, testes, and ovaries. Our focus is limited to estrogen, progesterone, testosterone, growth hormone, and thyroid. In health, all hormones are individually and wholly integral participants to the maintenance of cellular function

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and homeostasis. Hormone levels undergo diurnal variation and levels change in response to our environment, thought processes, stress levels, and food intake. Environmental toxins, medications, and pollutants also significantly affect hormone balance.

With the aging process, hormone levels decrease naturally. As these levels decline, problems with health maintenance arise. The diminution in hormone levels that occurs as a result of aging may or may not be compounded by concomitant disease states and environmental factors. In this article, we discuss age-related hormone loss and supplementation therapies for age-related hormonal deficiencies as possible first-line therapeutic modalities to be considered in our search to improve quality of life, prevent chronic illnesses, and maintain wellness.

ESTROGEN, PROGESTERONE, TESTOSTERONE

Scientists have determined the existence of three true end-organ sex hormones: estrogen, progesterone, and testosterone. Both men and women have all three hormones, although levels and ratios of these hormones vary according to gender.

Estrogen and progesterone are the dominant hormones in women. We are often faced with the misconception that estrogen, progesterone, and testosterone act independently of one another. Without fully understanding the inseparable nature of the interaction between all sex hormones, we cannot solve the problems caused by imbalances in their individual levels and the symptoms these imbalances cause.

Estrogen is made in the ovaries, the corpus luteum, adrenal glands, and fat cells. Estrogen is not one big molecule; rather, it is a group of molecules. In humans, the three main identified estrogen molecules are estriol, estradiol, and estrone.

Estradiol is the most active form of estrogen made by the ovaries, adrenals, and fat cells postmenopause. Estradiol directly affects a wide range of cellular functions, as estrogen receptors are ubiquitous.

Estriol is the weakest of estrogens. Estriol is primarily manufactured during pregnancy by the placenta. It attaches to cell receptors affecting hair, nails, and skin. Recorded data on estriol's function demonstrate that estriol's effects are limited mainly to the vaginal walls with a little effect on the heart and bones in nonpregnant women. In the nonpregnant, young, and premenopausal woman, estriol is made in the liver in small doses. Studies on the use of estriol in menopausal women and women with multiple sclerosis have demonstrated promising results.[1]

Estrone is manufactured in fat cells after menopause primarily from testosterone derivatives (androstenedione). Estrone levels tend to rise after menopause and the increase in estrone has been implicated in an increased incidence of breast tumors but most data have been obtained from animal studies. Overweight older women have high circulating levels of estrone.

When the scientific and lay communities refer to estrogen, they typically refer to its three components as one. At times, this oversimplification leads to errors in separating the individual function of the estrogens, particularly when discussing the differences between estrogen preparations used as hormone-replacement therapy available on the market. Although their actions are perceived and often recorded as one, the component molecules of estrogen have different potencies and effects.[2–6]

During the aging process, the ovaries stop producing estrogen on a regular basis. Thereafter the main source of estrogen is from the adrenal glands, primarily in the form of estrone. The body transforms unused testosterone into estrogen (primarily estrone) and releases estrogen stored in fat cells.

Estrogen and progesterone are antagonists. Their actions are designed to balance each other and keep each other in check.[7] We cannot live in a healthy state without hormonal balance. At no time do hormones act independently under normal circumstances in healthy bodies.[7] For example, estrogen increases cell proliferation in the endometrium, while progesterone inhibits cell proliferation. Without progesterone, endometrial hyperplasia occurs in the uterus.[6–8]

Progesterone is manufactured primarily by the corpus luteum (the follicle transformed after ovulation) and also to a small degree by the adrenals. In the ovary, progesterone production is activated at ovulation (15 days before the next menstruation),[7] stimulated by the release of luteinizing hormone from the pituitary gland and is crucial to the survival of the ovum once fertilized. When pregnancy occurs, progesterone production increases rapidly and its manufacture is taken over by the placenta. If a woman does not get pregnant, the corpus luteum involutes and progesterone production diminishes and eventually disappears in parallel with estrogen production, heralding menstruation.

Progesterone is a precursor to most sex hormones, including estrogen in the ovaries, testosterone, all androgens, and other adrenal hormones, making it an extremely important hormone for reasons far beyond its role as a sex hormone. Progesterone in the breast and uterus counteracts the stimulation of cell growth, which is a direct action of estrogen. It accomplishes this action by activating the progesterone receptor, which in turn, down-regulates the estrogen receptor. Because progesterone suppresses estrogen-driven cell proliferation, progesterone in the natural state helps keep breast cell growth in healthy balance.[9]

ESTROGEN AND PROGESTERONE: NOMENCLATURE, COMMERCIAL AVAILABILITY

Among the medications approved by the Food and Drug Administration (FDA) for hormone therapy are two classes of sex steroid hormones: estrogens and progestogens (which broadly include progesterone and progestogens or progestagens, also referred to as ''progestins'' or ''progestational agents''). For better clarification, these medications must further be divided into two groups: (1) bioidentical hormones with molecular structure identical to that of the human hormones and (2) preparations with molecular structures different from that of human hormones (nonidentical). The molecular difference between these two types of hormone formulations affect their actions in the human body.[2,4,7,10]

In 2001, a literature review by Stanczyk[5] scrutinized the various estrogen preparations available on the market. The investigator noted that the scarcity of comparative pharmacokinetic information between various formulas of estrogens created a void in our knowledge of their differential effects and thus hindered our ability to serve the patient. He encouraged comparative studies to help determine the best type of estrogen to be used as therapeutic options to enable individualized treatments and approaches that would fit each woman's risk profile and personal preference.

Hormone Preparations with Molecular Formulas Unlike Those of Human Hormones

Hormone preparations that are molecularly different from human hormones are the most commonly used and marketed hormone-replacement therapy in the United States. They are commonly referred to in the popular literature as synthetic estrogens or pregnant horse urine estrogens. The most popular estrogenic preparations in this category include such oral estrogens as conjugated equine estrogen (Premarin), esterified estrogen (Estaratab, Menest, Cenestin), estrone sulfate (Ogen), and ethinyl

estradiol (Estinyl); and such vaginal creams as estropipate (Ogen) and dienestrol (Ortho-dienestrol).

Progestins

Progestins, which include drug formulations that are also molecularly different from those for human progesterone, were developed to balance the endometrial hypertrophy associated with the use of unopposed conjugated estrogens on the uterus.[7–9,11,12] Progestins are chemical compounds manufactured with two types of primary characteristics: androgenic and nonandrogenic properties. Progestins are manufactured in the laboratory and are not extracted from any known animal sources. They include medroxyprogesterone (Provera, Amen, Cycrin), norethindrone (Micronor, Norlutin), and norethindrone acetate (Norlutate).

Combination Products

Combination products contain combinations of both estrogenic and progestogenic compounds. Some include one hormone that is molecularly identical to human hormones and one that is not, while some contain both the estrogen and the progestogens that are molecularly different from human estrogen and progesterone. They include conjugated estrogen (nonidentical) and synthetic progestin (nonidentical) (Prempro, Premphase);17-beta-estradiol (bioidentical) and norgestimate (nonidentical) (Orthopresfest); ethinyl stradiol (nonidentical) and norethindrone acetate (nonidentical) (FemHRT); and esterified estrogens (nonidentical) and methyltestosterone (nonidentical) (Estratest).

Bioidentical Hormone Preparations

Bioidentical hormones are manufactured to be molecularly identical to hormones found in the human body. Bioidentical preparations include estradiol, estriol, progesterone, and testosterone. Bioidentical hormones are available both in commercial and compounded forms. Bioidentical hormones are not a marketing term. The term has been used for more than a decade in the inserts to all FDA-approved commercial hormone preparations that contain hormones molecularly identical to human hormones. Commercially and compounded available bioidentical hormone preparations include:

17-Beta estradiol (Alora, Climara, Esclim, Estrace)
17-Beta estradiol patches (FemPatch, Vivelle-Dot, Vivelle, Estraderm)
Estradiol transdermal spray (Evamist)
Progesterone in peanut oil capsule (Prometrium)
Progesterone vaginal gel (Crinone)
Micronized progesterone in various compounded forms (capsules, troches, transdermal creams, vaginal suppositories)
Combinations of estradiol and progesterone in compounded formulations as above
Combinations of estradiol, estriol, and progesterone in compounded formulations as above

Beyond the commercial bioidentical hormone formulations, individually compounded preparations of bioidentical hormones are prepared in compounding pharmacies or laboratories (some are FDA approved; all are regulated by the state they operate in) on an individualized basis as prescribed by a physician. These products contain the same active estrogens, progesterone, and testosterone as those found in the commercial preparations listed above. The difference is that they are

individually mixed in tablet, capsule, troches, gels, or creams to the specifications of the prescribing physician for the individual patient. Unlike the commercial preparations, compounded hormone preparations are not manufactured on a large scale and can only be produced for individual patients as prescribed by a physician or other licensed practitioner, depending on the particular state rules.

In a recent review of bioidentical hormones in menopause, Boothby and colleagues[13] reviewed only the compounded formulations of bioidentical. The investigators made no mention of the commercially available bioidentical hormones. This omission inadvertently perpetuated the confusion, credibility, and even existence of bioidentical hormones in FDA-approved commercially available preparations.

Much of the confusion surrounding estrogen and progesterone formulations comes from the lack of clear distinction between their molecular formulas, the lack of focus on their different effects in the human body, and the use of nonspecific nomenclature when referring to estrogen and progesterone regardless of formulaic or activity differences.

The molecular differences between bioidentical and nonhuman identical hormone preparations are illustrated in (**Fig. 1**).

Controversy

The differences in behavior of various hormone formulations in vivo and vitro are directly connected to the differences in molecular structure as described in the scientific literature.[10,14–16] As early as 1976, scientific data demonstrating the safety of bioidentical hormones appeared in the conventional medical literature.[17] Reports of increased risk of endometrial and breast carcinoma among users of synthetic conjugated estrogens also appeared in the scientific literature.[3,8,9,11]

By January 1978, the *Journal of the American Geriatrics Society* addressed the growing concern that treatment with exogenous estrogen alone causes cancer and reported on progestogen as the solution. Adding small doses of a progestogen to either estradiol or conjugated estrogen in a cycled manner was determined to be a safe solution to the concern of increased carcinogenicity found with the use of unopposed estrogen.[18] It is noteworthy that, in 1983, the options for treatment studied included bioidentical estradiol and conjugated estrogens with medroxyprogesterone. The stated goal of the treatment was to help women feel better as they aged and ''not to harm'' them in the process.[19]

As early as 1980 and continuing into the recent literature, untoward side effects of synthetic progestins, such as thrombotic phenomena; breast tissue cell hyperplastic changes; and cardiovascular, cholesterol, carbohydrate, and lipid metabolism changes,[7,10,14] prompted more research into bioidentical (micronized) progesterone as a safer option. An article in the *British Medical Journal* in March 1980 noted: ''Clinically, oral bioidentical progesterone may be of value when synthetic progestogens have caused adverse symptoms that necessitate stopping treatment.''[20]

Recommendations for the use of bioidentical progesterone as a safer alternative were found in the medical literature from Europe as well as the United States throughout the early 1980s.[21–23]

In the 1980s and early 1990s, research scientists expressed concern that the synthetic progestins in hormone therapy could increase the risk of breast cancer.[24,25] About this same time, the scientific literature was replete with studies of safer alternatives in the form of bioidentical estradiol and progesterone, as well as studies comparing bioidenticals to the synthetic hormones and comparing various methods of administration with transdermal method of administration demonstrating the most promise in the area of safety and efficacy. Examples of such scientific literature

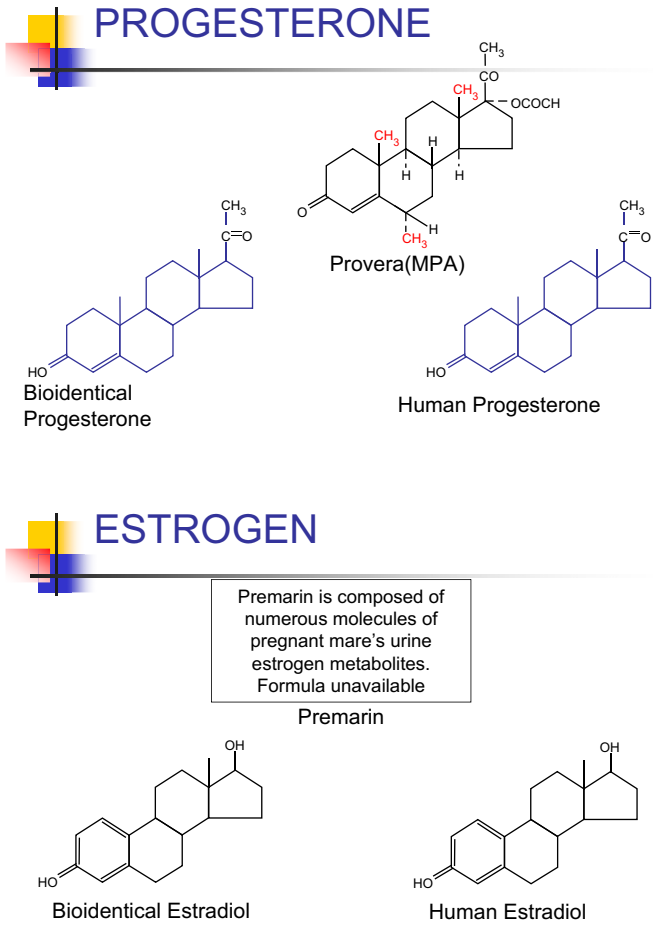

Fig. 1. The molecular formulas of various types of progestagens and estrogens. (*Adapted from* United States Pharmacopeia; and United States National Formulary.)

included an article by Foidart and colleagues,[12] who demonstrated that estradiol and progesterone had less proliferative effects on breast tissue cancer cell lines than did progestins and conjugated estrogens. Franke and Vermes[14] showed that progesterone-induced apoptosis in breast cancer cell lines that were conversely stimulated by synthetic progestins and other androgenic progestins. Place and colleagues[26] conducted a double-blind comparison of estradiol in transdermal form and Premarin that demonstrated improved relief of postmenopausal symptoms in the patient group on estradiol with no side effects. Riis and colleagues,[27] in a double-blind clinical controlled study, demonstrated that bioidentical estradiol and micronized progesterone helped improve bone density in postmenopausal women. Moorjani and colleagues[31] reported on the improved lipoprotein profile in patients receiving oral bioidentical estrogen with progesterone over those on progestins with androgenic action.[9–17,26–33]

Notably, the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, a long-term randomized trial of hormone-replacement therapy, compared multiple effects,

including cardiovascular effects, of both synthetic progestins and micronized progesterone in combination with conjugated equine estrogen. The PEPI trial confirmed that over the course of 3 years, oral conjugated estrogen taken alone or with synthetic progestins or micronized progesterone was associated with clinically significant improvement in lipoprotein profile and lowered fibrinogen levels. PEPI also demonstrated significant losses in high-density lipoprotein cholesterol when synthetic progestin was added (significantly reducing the beneficial effects of estrogen). However, when bioidentical progesterone was added, there appeared to be statistically significant endometrial sparing and the bulk of estrogen's favorable effects on risk factors, including high-density lipoprotein cholesterol, were also preserved.[34]

In 1994, the National Institutes of Health began the Women's Health Initiative (WHI), a large-scale prospective double-blind placebo-controlled study. The goal of the study was to evaluate the long-term effect of hormone-replacement therapy versus placebo in the prevention of heart disease, osteoporosis, cancer, and strokes in postmenopausal women. The only form of hormone-replacement therapy used in the study was conjugated equine estrogens (conjugated estrogen [Premarin]) and medroxyprogesterone (synthetic progestins [Provera]). Unfortunately, the WHI did not include a bioidentical arm even though bioidentical hormone usage and statistically significant studies consistently demonstrated positive results and sustainable safety and efficacy records for this therapeutic modality.[10,35–42]

Studies comparing the effectiveness and safety of different methods of administration (oral versus transdermal or vaginal),[26,27,29–33] the use of synthetic versus bioidentical replacement,[26,34,38,40] and the use of estrogen only versus combined estrogen and progesterone[10,34,37,40–42] have raised more questions about the logic and safety of using conjugated estrogen and synthetic progestins in our patients. Large-scale studies have been conducted in Europe where bioidentical hormone replacement therapy is the main type of hormone supplementation in menopausal women. These studies repeatedly demonstrated effective elimination of menopausal symptoms and a lack of long-term negative side effects with the use of bioidentical preparations. Foidart and colleagues[12] showed in a small study that, within 14 days, exposure to progesterone reduced the estradiol-induced proliferation of the breast epithelial cells in vivo in 40 postmenopausal women. E3N is a large prospective French cohort study that investigated breast cancer risk factors in 98,997 women born between 1925 and 1950. The data were analyzed every 2 years and the conclusion emerged that micronized progesterone regimens, compared to synthetic progestin regimens, were associated with significantly lower breast cancer risks. Additionally, women who took the hormone-replacement therapy consistently were at lower risk than women who took the hormones occasionally.[43] De Lignières and colleagues[44] reported the results of an 8.9-year study of a cohort of 3175 postmenopausal women using mainly transdermal estradiol and progesterone. No increased risk of breast cancer was found (risk ratio [RR] of breast cancer per year of use was 1.005). Stahlberg and colleagues[40] reported on the Danish Nurse Cohort Study commenced in 1993, which followed 19,898 women aged 45 and above. The highest risk of cancer was found in the women who used continuous combined estrogen with synthetic progestin. Nelson[41] reviewed the studies that evaluated the short-term effectiveness of conjugated estrogen and estradiol as treatments for relief of hot flashes. The conclusion was that they both have comparable short-term effects. The overarching problem with conjugated estrogen is the long-term increased risk of breast cancer, stroke, and myocardial infarction, which was proven by the WHI initiative.

This situation leaves us with the very important knowledge that hormone-replacement therapy is an important tool in wellness and prevention. The type of

hormone therapies we choose for our patients is what makes the difference and must be carefully considered.[10,12,21,22,25,40–44]

Risks/Benefits

Scientific reviews of the pharmacology and action of progestins demonstrate that all progestins and progestogens are not created equal, and their action varies significantly according to their molecular structure. In the studies reviewed, bioidentical progesterone proved to be safer and more effective in all trials that involved its usage[10,43,44] and numerous studies have shown that any estrogen (conjugated estrogen or bioidentical estradiol) combined with synthetic progestin doubles the risk of breast cancer.[28,45–49] Unlike synthetic progestins, bioidentical progesterone has been shown to have a consistently beneficial effect on breast cell proliferation.[50] The E3N and Danish Nurses studies, which address large populations taking various types of hormone-replacement therapy for more than 5 years, did not find progesterone to be an increased risk factor for breast cancer while progestin was. When estradiol was used in studies that evaluated its effectiveness in relieving menopausal symptoms, including hot flashes, night sweats, insomnia, and mood swings,[51,52] and in improving sleep patterns[53,54] and lipid profiles,[55] the results were consistently positive.

The WHI study came to an abrupt halt in July 2002 primarily because the interim data demonstrated increased risk of myocardial infarction, stroke, and breast cancer in the conjugated estrogen and synthetic progestin arm of the study.[56–59] Since that time, the suggestions to use hormone-replacement therapy in menopausal women has raised fears, doubts, and confusion. Millions of women, exposed to the media frenzy caused by the WHI's unsettling results, abruptly stopped taking their hormone therapies at the advice of their physician and on their own. This situation required physicians to rethink hormone-replacement therapy and to look at other options for relief. Much time and effort has been spent on reevaluating the results of the WHI. This reexamination has brought to light many questions about the validity of the findings and soundness of the study.[60–66] Despite questions raised about the validity of the WHI study, the study itself still provides grounds for caution. The use of synthetic estrogen and progestin replacement remains questionable at best.

Even though the only long-term study on hormone-replacement therapy in the United States was conducted on synthetic hormones and the data clearly established increased risk of cancers and strokes with the use of conjugated estrogen and progestins, hormone therapies are still the most effective therapeutic modalities for the elimination of symptoms of menopause and should be considered an integral part of the overall well-being of the aging woman. While in the short term, the type of hormones used may or may not be as significant as in the long run, the question is: What are the best options for the short and long terms for the women we treat?

An epidemiologic review of the rise in incidence in breast cancer in 1990 looked at the receptor status and the relationship to stage. Of interest is the fact that the investigator found that the incidence in older women increased and the cancers were more likely to be estrogen receptor positive. These cancers carry better prognosis because they tend to grow more slowly and are sensitive to hormonal manipulation.[25] This information is useful for the primary care physician when deciding therapeutic course of action over the long term.

Subsequent to the discontinuation of the WHI study, hormones that are synthetic and molecularly dissimilar to human hormones can no longer be prescribed without hesitation. A growing number of physicians involved in prevention and wellness, in response to concerns raised by the WHI and to requests and demands from patients,

have created study groups and forums within alternative and integrative medical organizations, have written books, and are conducting seminars sharing their clinical experience and research data on the use of bioidentical formulations of estrogen and progesterone. Risks associated with the use of conjugated estrogen and progestins, including the increased risks of breast cancer and cardiovascular events,[10,40,43–46,56–59] have not been reported with the use of bioidentical hormones.[50–55]

Based on the extensive scientific data we have reviewed for this article, it is unclear whether any absolute circumstance calls for synthetic versions of hormone-replacement therapy and such use appears unwise. Given the easy commercial availability of bioidentical formulations and the lack of negative data on these hormones, primary care physicians can easily access them for their patients. When faced with the need to treat a woman with hot flashes, night sweats, insomnia, mood changes, loss of libido, and other symptoms of menopause, the primary care physician must choose wisely the safest and most effective way of improving the quality of life for the patient. While further long-term randomized trials would be helpful to quantify the difference in RRs between synthetic and bioidentical hormone replacement over the long term, the current state of evidence demonstrates bioidentical hormones as a safe and effective option to be considered separate and distinct from its synthetic counterparts.

TESTOSTERONE

Female

Although estrogen remains the central female hormone most frequently used in both wellness and disease prevention, much less controversy surrounds the use of testosterone in women, though the evidence either supporting or discouraging its use is scarce. Nicknamed "the hormone of desire" and promoted in the popular media as the rescuer from the plight of decreasing libido in aging women, testosterone has gained rapid acceptance in the prevention and wellness arenas at a time when controversy and confusion surround estrogen and progesterone therapies.

Testosterone is produced by the ovaries and adrenals in young women in low doses (free testosterone levels range between 2–8 pg/mL). The bulk of the present research on the use of testosterone has been conducted on women with surgical menopause, hypopituitarianism, anorexia nervosa, and primary adrenal insufficiency; patients with HIV and low body weight;[67] and patients with glucocorticoid- and oral contraceptive–induced suppression of endogenous androgens. There has been little if any formal study on testosterone use in normal aging in women.

Benefits

Muscle mass The addition of testosterone to conjugated estrogen results in an increase in fat-free body mass and mitigates central fat deposition associated with estrogen use.[68,69] In a double-blind placebo-controlled small study of androgen-deficient women, testosterone replacement demonstrably increased thigh muscle mass as measured by CT scanning.[70] The data is very limited and its value and usefulness on large populations unknown. Further evaluation and research must be conducted as we address the possibility of usage of testosterone in the aging female to help improve muscle mass and decrease central adiposity.

Libido Loss of libido in the aging female is the most common complaint that leads physicians to consider testosterone deficiency as a possible cause and the main consideration for treatment with testosterone. Multiple factors directly affect sexual inclination. Poor relationship status, self-image issues, multiple medications and their

side effects, other stress factors, aging, and concurrent chronic or acute illnesses are some of the most frequently encountered deterrents of sex drive. Many of these factors cannot be altered, and all factors should be taken into account. Even so, testosterone appears to be effective in offsetting some of the effects from these factors, leading primary care physicians involved in integrative and wellness practices to make testosterone supplementation more popular.

Lack of training in the area of loss of libido and lack of concrete diagnostic criteria have created difficulties for the primary practitioner when attempting to address this problem. While circulating testosterone levels are not very helpful in diagnosing low testosterone as the cause for loss of libido, it may be helpful to keep in mind that premenopausal women have a range of 20 to 75 ng/dL total testosterone while postmenopausal women can present with values as low as 5 to 10 ng/dL. Because we rarely have comparative levels of testosterone on a patient before they come in with the complaint, it is almost impossible to determine whether the testosterone levels correlate in any way with the appearance of symptoms.[71]

The seminal study on impaired sexual function improvement with supplemental testosterone comes from oophorectomized women. Seventy-five women 31 to 56 years old postoophorectomy and -hysterectomy were randomly assigned to receive conjugated estrogen and various doses of transdermal testosterone. The women who received the higher dose of testosterone reported a two- to threefold increase in sexual desire, masturbation, sexual intercourse, and sense of positive well-being as compared with placebo or conjugated estrogen alone.[72]

Breast cancer Acting through androgen receptors, testosterone opposes estradiol-induced proliferation of human breast cell lines.[73] Cases where endogenous testosterone levels are elevated, such as with polycystic ovary syndrome, are associated with breast tissue atrophy and a decreased risk of breast cancer.[74] There are, however, conflicting data on the potential role of supplemental testosterone in the development of breast cancer and under no circumstances should testosterone be given without regular follow-ups.

Testosterone replacement considerations

Variation in dosing, method of administration, and duration of treatment are important determinants of safety and efficacy. To date, the medical literature contains little data on this topic. One is left with a smattering of information to help the patient rely on hopeful but dubious information obtained on the Internet and from popular literature.

Under these circumstances, a growing number of physicians involved with menopausal women's wellness are using testosterone supplementation to provide improvement in libido and mood simply based on clinical findings and blood levels. A popular literature book *The Hormone Of Desire* by Susan Rako, MD, published in 1999, was followed by hundreds of articles in popular science that led to the rise of testosterone supplementation as a potentially helpful resource in the plight of aging women.

Formulations

Testosterone formulations include testosterone gel (Androgel), which is not FDA-approved for women, and various compounded formulations of testosterone in cream, subcutaneous pellets, oral, and sublingual forms. In summary, though treatment with testosterone in the aging woman is gaining popularity, there is a definitive need for studies specific to this population to evaluate the safety and efficacy of testosterone as a therapeutic modality for postmenopausal women, as well as for younger women with loss of libido, to define its best use in prevention and wellness. Studies are

needed to help determine the safest and most efficacious methods for aging females to use testosterone.

Male

Testosterone is the primary androgen produced by the testes and it plays an essential role in the health of the male. Beyond determining the male sex characteristics, testosterone is a determinant of muscle strength, bone mass, libido, potency, and spermatogenesis.

Androgen deficiency

Androgen deficiency includes but is not limited to symptoms of decreased body hair, reduction in muscle mass and strength, increase in fat mass, decreased hematocrit, decreased libido, erectile dysfunction, infertility, osteoporosis, depression, and mood changes. Androgen deficiency may occur secondary to testicular or pelvic trauma or surgical removal, hypogonatropic hypogonadism, or with normal aging.[75]

The normal aging process leads to adult hypogonadism with a decrease in levels of testosterone with age and the development of some or all of the symptoms enumerated above. The condition of androgen deficiency in aging is also known as andropause.

Androgen deficiency or hypogonadism is the result of subnormal production of testosterone by the testes. Its prevalence in healthy males over the age of 40 is demonstrated in observational studies, but there is no agreed upon blood level that defines deficiency.

Common causes of hypogonadism include but are not limited to:

Primary testicular failure
- Klinefelter syndrome
- Cryptorchidism
- Orchitis
- Trauma
- HIV/AIDS
- Myotonic muscular deficiency
- Retroperitoneal fibrosis
- Aging

Hypogonadotropic hypogonadism
- Kallman syndrome
- Prader-Willi syndrome
- Idiopathic hypopituitarism
- Pituitary tumors
- Suprasellar tumors
- Hemochromatosis
- Inflammatory, traumatic, vascular lesions of pituitary and hypothalamus
- Obesity
- Severe chronic illnesses
- Medication
- Andropause

The risk of having low testosterone levels is significantly higher in men with hypertension (RR 1.84), hyperlipidemia (RR 1.47), diabetes (RR 2.09), obesity (RR 2.38) and asthma or chronic obstructive pulmonary disease (RR 1.40) than in men without these conditions. The prevalence of hypogonadism (defined as a total testosterone level below 300ng/dL) in 2162 men aged 45 years or older presenting to primary care offices was 38.7% in a study by Mulligan and colleagues.[76]

Controversy

Perhaps the most significant controversy related to testosterone is the debate over its role in prostate health. For more than 60 years, traditional medical wisdom regarded testosterone as a significant risk factor for prostate hypertrophy and assumed that high testosterone levels served as fuel for prostate cancer. Hormone blockade and or estrogen therapy are still standard of care for prostate cancer therapy even today. Clinicians have hesitated to treat aging males with testosterone because of the belief that high levels of testosterone cause prostate cancer or speed up its growth. More than a decade ago, Shippen, Fryer, and Wright took the view that testosterone is actually protective and should be used.[77] A ground-breaking study released in November 2007 provided a whole new set of data and a new perspective on testosterone.[78] The results of this large-scale prospective study revealed that high endogenous levels of testosterone are associated with low mortality from all causes. The study suggests that low testosterone may be a predictive marker for those at high risk of cardiovascular disease.

Shores and colleagues[79] investigated the correlation between testosterone levels (defined as total testosterone <250 ng/dL or free testosterone <0.75 ng/dL) and mortality in 858 males followed for up to 8 years. The results demonstrated that men with low circulating levels of testosterone had an 88% increased risk of mortality.

Benefits

Cardiovascular Experimental studies suggest that androgens induce coronary vasodilatation. A placebo-controlled double-blind (PCDB) study performed in the United Kingdom followed 46 men with stable angina randomized to receive either a 5-mg testosterone patch or placebo in addition to their current medicines for 12 weeks. Both groups were then monitored for changes in treadmill exercise time before the onset of myocardial ischemia. The results of the treatment group compared with the placebo group were statistically significant (22% improvement in exercise time before onset of ST depression) without effect on prostate-specific antigen (PSA), hemoglobin, lipids, or coagulation profile during the duration of the study. Low-dose supplemental testosterone treatment in men with chronic stable angina increased exercise time preceding induced myocardial ischemia as defined by ST depression on EKG.[80] Testosterone replacement therapy has also been proven to reduce insulin resistance, visceral adiposity, and cardiovascular risk.[81–83] Additionally, a relatively low testosterone, independent of adiposity, is a risk factor for insulin resistance and type II diabetes and vice versa (insulin resistance and diabetes mellitus II are risk factors for low testosterone).[84–86]

Anemia Anemia is a frequent feature of male hypogonadism and antiandrogenic therapies. In a study that evaluated hemoglobin levels in 905 persons 65 years or older, of which 31 men and 57 women had anemia, hemoglobin levels were evaluated after 3 years. The participants were patients without cancer, renal insufficiency, or antiandrogenic treatments. Statistical evaluation of the results showed that older men and women with low testosterone levels had a higher risk of anemia.[87]

Mood and quality of life There is a compelling need for therapies that prevent Alzheimer's disease, defer its onset, slow its progression, and alleviate its symptoms. In a study that evaluated the effects of testosterone therapy on cognition, neuropsychiatric symptoms, and quality of life in male patients with Alzheimer's disease and healthy elderly men, 16 male patients with Alzheimer's disease and 22 healthy male controls were treated with testosterone and a placebo gel daily. Patients receiving testosterone had significant improvement in quality-of-life scores and the treatment was well

tolerated. Testosterone had minimal effects on cognition and the treated group showed more numerical improvement and less decline in visuospatial functions.[88]

Osteoporosis and musculoskeletal Untreated hypogonadism is a prominent cause of osteoporosis in men[89] and bone mineral density significantly increases with testosterone treatment.[90] Older men are as responsive to the anabolic effects of testosterone as young men. Testosterone induces skeletal muscle hypertrophy that leads to improved muscle strength in the leg as demonstrated in this study. A reciprocal change in lean and fat mass is observed but further studies are needed to determine the exact mechanism of change and the therapeutic doses needed for older men to obtain optimal results with minimum side effects.[91]

Libido and sexual function Treatment with testosterone improved sexual function in hypogonadal males in this very small study as measured by frequency and duration of erection and frequency of ejaculation.[92–95] More studies in this important area must be undertaken to provide much-needed information. Perceived risks associated with testosterone treatments and its abuse in the areas of athletic enhancement have caused much confusion without scientific basis.

Risks

Prostate cancer The connection between higher testosterone levels and growth of prostate cancer originated in 1941 with the publication of two papers by Huggins and colleagues.[96,97] The data reported were based on one patient and, despite 67 years of subsequent studies that failed to establish scientific support for this theory, we are still faced with reluctance to treat men with testosterone supplementation for fear of giving them prostate cancer or fueling prostate cancer already present at a subclinical or microscopic level.

More than 430,000 men were part of longitudinal studies over the course of the past 67 years, and no well-designed study has ever shown a direct correlation between total testosterone levels and prostate cancer. A 2007 review out of Harvard concluded that:

> *Although there is yet to be a large, long term, controlled study on the effect of TRT [testosterone replacement therapy] on PCa [prostate cancer] risk, it should be abundantly clear that raising T [testosterone] in hypogonadal men has little, if any, impact on PCa risk or growth in the short to medium term. The withholding of TRT in men because of fear of PCa risk or progression is no longer tenable in an age of evidence-based medicine, because neither evidence nor theory supports this position.*

This article reviewed the state of the evidence and, based on the prospective longitudinal studies, concluded that "men who develop prostate cancer do not have higher baseline testosterone levels and men with higher testosterone levels are at no greater risk for developing prostate cancer than men with lower testosterone levels."[98]

The primary care physician needs to address each patient individually and decide on the use of testosterone based on more than just testosterone levels or fear of prostate cancer. Follow-up with serial blood tests and PSAs is still an important part of the clinical follow-up and should be used for the protection of the patient.

Aromatase One of the most important factors affecting testosterone levels in aging men is the enzyme aromatase, which is found in fat tissue. Aromatase converts testosterone into estrogen, thus changing the ratio of estrogen to testosterone.[99,100] Men who have excessive body and abdominal fat are likely to have increased estrogen

levels caused by aromatase activity. This condition has been linked to decreased insulin sensitivity and metabolic syndrome.[100]

Diagnosis

When a history and symptoms of hypogonadism are clear, the diagnosis is relatively easy. However, often the patient presents with nonspecific history and symptoms and an unremarkable clinical history, making the diagnosis more difficult. Clinically, the typical adult hypogonadism patient is above 50, fatigued, has difficulty building muscle in spite of consistent workout regimen, complains of unexplained weight gain, may be mildly depressed, and may experience erectile dysfunction and loss of libido. In this clinical setting without diagnosable disease, the diagnosis of a relative age-related adult-onset hypogonadism is gaining popularity and treatment with testosterone is becoming more common in the integrative medicine and urology fields.

Thus, it becomes important for the primary care physician, who is the first line of diagnosis and treatment, to feel comfortable with the use of testosterone as a viable and safe short- and medium-term option in the therapeutic armamentarium of healthy aging and wellness preservation. Understanding and considering hypogonadism in every adult aging male is an integral part of prevention and wellness.

Primary testicular failure is associated with elevated follicle-stimulating hormone and luteinizing hormone levels. A baseline PSA and a complete blood cell count should be obtained before starting testosterone supplementation. Estrogen, progesterone, and dihydrotestosterone levels may also be of value.

There is no agreed total or free testosterone cut-off level to define testosterone deficiency.[101] Total testosterone is the most common measure of androgen activity, but is a poor indicator of tissue activity, demonstrating little correlation with clinical status, and is an unreliable indicator of response to therapy.

Free testosterone is a more accurate indicator of hypogonadism,[102] but normal ranges for total and free testosterone vary widely among laboratories, even among those using the same assay, and the reference ranges show little or no correlation to clinical findings.[103] When testing the testosterone levels of a patient who is considering testosterone supplementation to maintain and improve wellness, it is unusual to have available prior testosterone levels when that patient was younger, healthier, and symptom free. Thus, a result that appears to be within normal range may not necessarily reflect what is normal for that particular patient. This situation must be taken into account since it emphasizes the importance of clinical assessment and patient involvement in the decision to treat.

The use of population-based statistically determined normal testing ranges is also limited by the fact that the average testosterone level in men today is less than the average level in men of the same age 15 years ago. This concerning fact is possibly due to environmental suppression of the hypothalamic-pituitary-testicular axis[104] and may also be a contributing factor to diminished sperm counts and increased incidence of infertility.[105]

Testosterone levels decrease with age and illness. Typically, men with hypogonadotropic hypogonadism have low plasma testosterone and luteinizing hormone levels. Prolactin levels should be checked if the total testosterone level is below 250 ng/dL to rule-out a pituitary tumor.

Fifty percent of circulating testosterone is bound to sex hormone–binding globulin, which directly affects free testosterone levels. Free testosterone levels can be obtained to clarify testosterone status. However, variations are greater among free testosterone assays than among total testosterone assays. Also, reference ranges are not as standardized for free testosterone assays as they are for total testosterone

assays. When borderline levels of testosterone are found, or the clinical picture and the blood tests disagree, a low or low-normal free or total testosterone level may be used to support a clinical diagnosis of androgen deficiency, but should not be used to exclude it.[101]

Treatment

Testosterone supplementation has gained popularity over the past 20 years. The benefits of testosterone supplementation include improved energy, greater muscle mass, increased stamina, greater strength, increased confidence, greater motivation, and enhanced libido.[102–106]

Present formulations of testosterone include the following:

Testosterone gel (Androgel)
Testosterone patches (Androderm)
Compounded testosterone creams or gels
Injectable testosterone
Subcutaneous testosterone implants

Monitoring

While it is useful to follow PSA levels during the course of testosterone replacement and supplementation, it is more important to track the velocity PSA increase. There is often a slight bump, a rise above 4.0 ng/mL, or a sudden increase in PSA with the initiation of testosterone therapy, followed by a stable constant level. An increase in PSA more than 0.35 ng/mL per year warrants further evaluation and a referral to the urologist.[107]

While using testosterone in disease prevention and wellness is relatively new to the primary care field, it holds much promise and meets with much support and enthusiasm from patients. The data we reviewed and our clinical experience support the use of testosterone as a first-line hormone supplementation in the aging male. More research is needed to substantiate and define the parameters necessary for its long-term use.

For now, as the esteemed Dr. Morgantaler said:

> *… the diagnosis of androgen deficiency requires only an ear attuned to the characteristic symptoms and blood test providing evidence of reduced levels of total or free testosterone. Treatment provides an opportunity for gratifying results, for patients and clinicians alike.*[108]

GROWTH HORMONE

As the proportion of aging people continues to rapidly rise, reducing the burden of age-related diseases becomes increasingly important in primary care. A controversial hormone that is center stage in the debate over the use of hormone therapies in prevention and wellness is growth hormone.

Growth hormone, a single-chain polypeptide produced in the pituitary gland, has a wide range of metabolic and cellular effects. Growth hormone plays an important role in the regulation of body composition, lipid profiles, tissue repair, cardiac and neuronal functioning, and maintenance of bone mineral density. Growth hormone is secreted in pulsatile fashion, especially during stage III and IV deep sleep. It acts on liver and other tissues to stimulate the production of insulinlike growth factors (IGFs), including IGF-1, which is also known as somatomedin C, and the production of IGF-binding proteins (IGFBPs), which also have direct cellular actions. The most abundant IGFBP is IGFBP-3.

A large percentage of growth hormone effects are mediated through IGF-1. Because of the pulsatile nature of growth hormone production and short half-life (20–50 minutes), routine serum growth hormone levels cannot be used to determine overall production. While there are many influences on the production of IGF-1, levels correlate with overall growth hormone production, are relatively stable in the serum, and are currently the best estimate of growth hormone production and effect. While a low IGF-1 is a strong indicator of abnormally low growth-hormone production, an IGF-1 level in the normal reference range does not rule out deficiency.[109]

While there is considerable variation in growth hormone production among individuals of the same age, there is a progressive decline in average growth-hormone production and IFG-1 levels after age 20, with average levels declining by 30% to 60% by age 40 to 60, and by 50% to 80% after age 60.[110–114] Low growth-hormone levels and production are associated with low quality of life as measured by numerous criteria, including the Nottingham Health Profile and the Psychologic General Well-Being Index.[113,115–118] Gibney and colleagues[119] reviewed 10 years of use of growth hormone in adult growth-hormone deficient patients and found it to be of significant benefit.

A large number of peer-reviewed research, including long-term randomized controlled trial data, has demonstrated that growth hormone replacement improves energy,[119,120] strength,[119] cardiac function,[121–123] blood pressure,[124] cholesterol levels,[124–126] insulin sensitivity[124,127] cognitive function,[128,129] immunity,[130,131] and psychologic well-being;[113,116,118,126] decreases body fat;[121,124,125,127–133] increases lean muscle;[121,124,132] prevents and reverses heart disease;[121,134,135] prevents and improves osteoporosis;[121,125,136] and improves quality of life.[116,118,119,126]

Controversy

Controversial issues regarding growth hormone supplementation include the use of growth hormone as a therapeutic modality for age-related deficiency; the accuracy and necessity of commonly used stimulation testing when considering growth hormone usage in well patients; the need for guidelines for safe and effective treatment; and potential side effects of treatment.

Diagnostic Testing

The diagnosis of growth hormone deficiency is difficult for a number of reasons. As discussed, random serum growth-hormone levels are not indicative of the overall growth hormone production and, while IGF-1 levels do correlate with overall growth hormone production, IGF-1 levels lack sensitivity to detect significant deficiency (IGF-1 levels are often in the normal range even if a significant deficiency exists).

With growth hormone stimulation testing, serum growth-hormone levels are measured after a variety of agents and protocols are used to stimulate the release of growth hormone from the pituitary. Such tests are often promoted as the means of differentiating growth hormone deficiency from normal state. Many endocrinologists believe the diagnosis of adult growth-hormone deficiency can only be made with the use of growth hormone stimulation testing. Such testing has proven to be inaccurate, highly variable, nonphysiologic, and lacking adequate sensitivity to detect relative growth-hormone deficiencies. The use of arbitrary cutoffs to define abnormality does not correlate with response to therapy.[137–145] Studies demonstrate that using the same agent to perform stimulation tests multiple times on one patient do not consistently produce congruous results, thus bringing the usefulness of the test into question.[138,139] Side effects of stimulation testing include significant hypotension, venous thrombosis, nausea, and vomiting.[129] Deaths and neurologic damage have also been reported.[134]

Because stimulation tests are clinically and physiologically unreliable, they are also unreliable for determining growth hormone deficiency. Currently the most appropriate means of diagnosing age-related growth-hormone deficiency is clinical recognition and a low-normal (below the mean) IGF-1 level.

Clinical Diagnosis

The adult age-related clinical syndrome of growth hormone deficiency includes increased fat mass, decreased muscle mass and strength, decreased bone density, elevated lipids, insulin resistance, decreased psychosocial well-being and depression, fatigue, increased social isolation, inability to handle stress, cardiovascular disease, memory decline, overall deterioration in quality of life, frailty, thin dry skin, increased wrinkles, and diminished exercise tolerance.

Clinicians commonly encounter these clinical symptoms in the aging patient. If considered appropriate by physician and patient, a 6-month therapeutic trial with growth hormone could be considered, dosed to keep IGF-1 levels in the upper quartile. Patients should be evaluated for symptomatic and metabolic improvements at a minimum at 3 and 6 months to decide if treatment should be continued.

Treatment

The treatment of age-related adult growth-hormone deficiency remains controversial even though the literature reports significant benefits from growth hormone supplementation. The main sources of concern associated with growth hormone replacement in somatopause include, in no particular order, significant cost of therapy from $250 to $1500 per month (depending on dose and manufacturer), side effects of water retention resulting in joint pain and carpal tunnel syndrome, temporary reduction in insulin sensitivity, and theoretic risk of cancer. Most short-term side effects are diminished with reduction in dose.[146–148]

While there is a long-held theoretic belief of an increased risk of cancer, based on the growth hormone's antiapoptotic and mitogenic effects, neither long-term nor short-term data support this theory. Conflicting data on the relationship between IGF-1 levels and the risk of cancer abound. Some frequently cited epidemiologic studies have found an increased correlation between elevated IGF-1 and breast,[149] prostate,[150] and colorectal cancers,[151] while the majority of studies failed to document increased risk of cancer (or have shown a decreased risk) with increasing IGF-1 levels.[152–165] In addition, one frequently cited study that did connect increased IGF-1 levels and cancer, by Chan and colleagues,[150] is very controversial because the blood was stored for 5 to 15 years before it was tested. Also, IGF-1 levels in the highest quartile group were over three times the upper limit of normal for this age group, suggesting that IGF-1 in the patients studied may not have been measured accurately. Hankinson and colleagues[149] found a trend for decreased risk of breast cancer in postmenopausal women with increased IGF-1 levels but an increased risk in premenopausal women. Palmqvist and colleagues[151] reported increased association between IGF-1 and colon cancer, but a decreased risk of rectal cancer.

The secretion and regulation of IGF-1 is extremely complex and their reported association with cancer must also take into consideration numerous other potential confounding etiologic factors, whether environmental, nutritional, or other yet unidentified. Growth hormone stimulates the production of IGFBP-3, which has cancer-protective characteristics and may counteract increased risk of cancer associated with an increase in IGF-1, if present. There is evidence that tumors secrete IGF-1, which makes it a potential marker for cancer in some individuals and not necessarily a cause. Typical growth hormone supplementation for an age-related deficiency

results in small increases in IGF-1 that remain in the normal age-matched references range, so risk would not be expected to be different than that for controls.

None of the long- and short-term studies have shown an increased risk of cancer, recurrent or de novo, with the use of growth hormone,[166–177] and some of the studies have shown a decreased risk. Among these studies are studies on more than 19,000 children representing of 47,000 patient years of growth hormone treatment;[176] a prospective study of 100 adult growth hormone–deficient patients followed for 1 to 4 years,[177] a study of 910 children treated with growth hormone for 11 years,[175] a study of 32 adults and children followed for up to 40 years treated with growth hormone (average 10.8 years);[166] a study of 180 growth hormone–treated children followed for over 6 years with reduced cancer recurrence risk (RR 0.6);[169] a prospective analysis of 289 growth hormone–deficient adults who, after 5 years of growth hormone therapy, showed lower risk of malignancy (RR 0.25) and decreased risk of myocardial infarction (RR 0.19) and early mortality (RR 0.22) compared with the untreated group.[172]

In 2001, the consensus statement by the Growth Hormone Research Society noted that the data demonstrate that the concern for increasing the risk of cancer with the use of growth hormone is unfounded:

> *The current labeling for GH [growth hormone] states that active malignancy is a contraindication of GH treatment. There are, however, no data to support this labeling. Current knowledge does not warrant additional warning about cancer risk on the product label.*

Supraphysiologic doses of growth hormone are shown to antagonize the effects of insulin. While short-term studies using large doses of growth hormone may potentially worsen insulin resistance,[178] low physiologic doses of growth hormone have demonstrated improvement in insulin resistance and decreased risk of diabetes.[179–182] If treatment is contemplated, low physiologic doses should be used to keep IGF-1 in the upper limit of normal.

In conclusion, aging adults have a relative deficiency of growth hormone and supplementation with growth hormone may be of significant benefit. A clinical diagnosis of growth hormone deficiency can be made with support of low-normal IGF-1 levels alone. Although no long-term studies have assessed side effects with low physiologic doses of growth hormone supplementation in somatopause, the studies we reviewed above have confirmed that low doses, titrated to keep IGF-1 levels in the upper limit of normal, are safe, well tolerated, and associated with a plethora of clinical benefits.

Treatment with growth hormone is presently limited to an affluent and highly motivated population. Cost and risk/benefit ratio over time must be taken into consideration. As our patients age, the challenge of maintaining quality of life for them becomes more difficult and must be considered in the design of future studies. For supplementation with growth hormone to become a first-line therapeutic option in the aging population, additional and more extensive randomized trials that evaluate results of growth hormone treatment in age-related deficiency must be undertaken, and cost factors must be addressed.

THYROID

Hypothyroidism is a common disorder with inadequate amounts of thyroid hormone present at the cellular level. Typical symptoms include fatigue, weakness, weight gain, cold intolerance, muscle aches, headaches, decreased libido, depression, hair

loss, and dry skin. Signs include edema, dry skin, pallor, hair loss, loss of temporal eyebrow hair, and cold extremities. Conditions associated with hypothyroidism include hypertension, atherosclerosis, hypercholesterolemia, hyperhomocysteinemia, menstrual irregularities, infertility, premenstrual syndrome, chronic fatigue syndrome, fibromyalgia, fibrocystic breasts, polycystic ovary syndrome, depression, diabetes, and insulin resistance.

There is a two- to threefold increase in the incidence of thyroid dysfunction with age, including overt and subclinical hypothyroidism (elevated thyrotropin with normal thyroxine and triiodothyronine levels).[183] There is also an age-related decrease in thyroid function that results in diminished tissue thyroid levels and may result in clinically symptomatic hypothyroidism that is not detected with the standard use of thyrotropin, thyroxine, or triiodothyronine levels.

Historically, an elevated thyrotropin with normal thyroxine and triiodothyronine levels has been considered compensated or subclinical hypothyroidism and diagnosed as euthyroid with no requirement for treatment. A plethora of studies have, however, demonstrated that, in spite of the normal triiodothyronine and thyroxine values, subclinical and nondiagnosed hypothyroidism is often associated with significant symptoms and an increased risk of morbidity and mortality.[184–211] In light of this, it has been proposed that the term subclinical hypothyroidism be replaced by the term mild thyroid failure (MTF).[184]

The diagnosis of MTF is particularly important in the aging population in the areas of prevention and wellness. MTF is a treatable condition associated with increased cardiovascular risk and numerous signs and symptoms that might otherwise be attributed to "usual" signs and symptoms of aging, including fatigue, depression, memory loss, cognitive dysfunction, dry skin, constipation, leg cramps, cold intolerance, weakness, water retention, diminished sweating, weight gain, and diminished exercise tolerance.[184–211] Significant improvements may occur with treatment.[185,190,192,193,196,198,202]

Numerous studies have demonstrated increased cholesterol levels in patients with MTF.[184,202,206,207,211] Thyroid replacement results in a significant reduction in the cholesterol levels.[205–207] In addition to the increase in total and low-density cholesterol seen with MTF, endothelial dysfunction with impaired vasodilatation have also been demonstrated, further increasing the risk of cardiovascular events.[210]

The Rotterdam study investigated the association between MTF and aortic atherosclerosis and myocardial infarction in 1149 menopausal women. After adjustment for multiple known coronary artery disease risk factors, the investigators found that MTF significantly increased the risk for arthrosclerosis (odds ratio 1.9) and myocardial infarction (odds ratio 3.1).[204] This important study found that subclinical hypothyroidism was a greater risk for myocardial infarction than hypercholesterolemia, hypertension, smoking, or even diabetes, and that MTF was a contributing factor in 60% of the myocardial infarctions in the patients studied.

In a 20-year longitudinal study, Walsh and colleagues[211] also examined the association between MTF, cardiovascular disease, and mortality in over 2000 individuals (approximately half men and half women) with a mean age of 50 years (age range 17–89). In this study, MTF was associated with a 2.2-fold increased risk of coronary artery disease and 1.5-fold increased risk of cardiovascular mortality after adjustment for multiple known cardiovascular risk factors.

Diagnostic Testing

Thyrotropin is considered the most sensitive marker of peripheral tissue levels of thyroid hormone, and it is widely assumed that thyrotropin levels within the normal

range indicate the person is euthyroid. With significant physiologic stress, illness, inflammation and aging, however, there is demonstrable suppression of thyrotropin, making the thyrotropin test unreliable.[212–231] With significant physiologic stress, illness, inflammation, and aging, tissue-specific alterations also reduce tissue triiodothyronine levels by reducing uptake of thyroxine into tissues and decreasing thyroxine-to-triiodothyronine conversion.[217–228] The decreased serum thyroxine levels caused by the suppressed thyrotropin production is offset to varying degrees by the diminished uptake of thyroxine into the cell and the decreased thyroxine-to-triiodothyronine conversion. This situation tends to be misread as an indication of adequate tissue thyroid levels and makes thyroxine levels of little use, except in extreme cases.[223–225]

With physiologic stress, inflammation, illness, and aging, the correlation between serum thyrotropin and thyroxine levels and peripheral thyroid activity no longer follows.[212–231] Thyrotropin and thyroxine levels cannot be relied upon to detect diminished cellular triiodothyronine levels for aging patients and patients under stress. Instead of thyroxine normally converting intracellular to the active triiodothyronine in peripheral tissue, thyroxine is preferentially converted to reverse triiodothyronine. Serum reverse triiodothyronine levels may be useful because diminished cellular uptake of thyroxine, diminished thyroxine-to-triiodothyronine conversion, and diminished cellular triiodothyronine levels inversely correlate with serum reverse triiodothyronine levels.[212,222,223,225,229,230]

When the physiologic stress or illness is acute and severe, the significantly diminished thyroid levels in the peripheral tissues no longer correlate with thyrotropin levels. This is termed nonthyroidal illness or euthyroid sick syndrome. In these cases, the thyrotropin level cannot be relied upon as an accurate measure of tissue thyroid effect.[212,213,226] The same physiologic changes also occur with chronic physiologic stress, chronic illness, inflammation, calorie reduction, and aging.[216–245] Changes can be metabolically significant and can cause serious symptoms. Treatment may be warranted despite normal thyrotropin and thyroxine levels.[224,235,246,247] The use of thyroxine preparations in the treatment of nonthyroidal illness found in acute conditions, such as trauma, surgery, and sepsis, has shown little benefit. The ineffectiveness of thyroxine preparations in these cases is most likely due to the diminished use and uptake of thyroxine in these conditions. In contrast, treatment with triiodothyronine has proven quite beneficial in studies of severely ill patients,[247–252] as well as in chronic conditions,[246,253–255] which correlate well to the aging patient.

Similar to significant physiologic stress and illness, aging is associated with significant alterations in the hypothalamic-pituitary-thyroid axis that result in a reduction of thyrotropin levels[244,250] (in contrast to MTF's increase in thyrotropin) while tissue-specific alterations reduce the supply of triiodothyronine (via reduced thyroxine-to-triiodothyronine conversion and reduced uptake of thyroxine) to the body tissues.[244,256–262]

With aging, as with nonthyroidal illness, thyrotropin and thyroxine are not indicative of tissue levels of triiodothyronine, making the interpretation of thyroid function tests increasingly complicated and difficult. Aging may be considered a chronic nonthyroidal illness leading to decrease in basal metabolic rate[259,263,264] and reduction in thyrotropin and triiodothyronine levels without a significant decrease in thyroxine and free thyroxine[244,256–258,261,262] (**Fig. 2**). Elevation in reverse triiodothyronine level is also seen[240,244,265,266] as a consequence of diminished use of thyroxine, diminished thyroxine-to-triiodothyronine conversion, and diminished tissue levels of triiodothyronine.[212,222,223,225,232] Another finding in the aging patient is the significantly reduced thyrotropin response to thyrotropin-releasing hormone

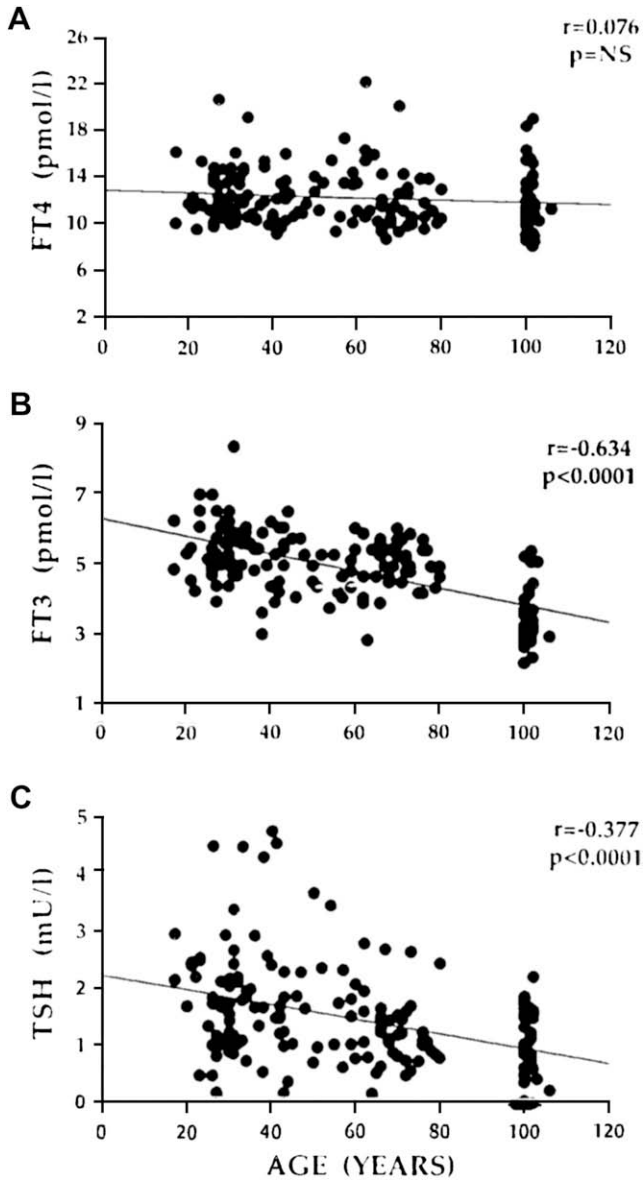

Fig. 2. Age-dependent variations in (*A*) free thyroxine (FT4), (*B*) free triiodothyronine (FT3), and (*C*) thyrotropin (TSH). All healthy subjects in the study (groups *A*–*C*) were pooled for this analysis. (From Mariotti S, Barbesino G, Caturegli P, et al. Complex alteration of thyroid function in healthy centenarians. J Clin Endocrinol Met 1993;77(5):1132; with permission. Copyright © 1993, The Endocrine Society.)

that is similar to that found in severely ill patients with documented nonthyroidal illness.[260,262,267]

Further contributing to potential inaccuracies of standard thyroid testing in this population is the increasing incidence of systemic illness and the increased use of medications that directly affect thyroid function. In aging patients who present with

symptoms consistent with hypothyroidism but have a normal thyrotropin and thyroxine level, obtaining free triiodothyronine, reverse triiodothyronine, and triiodothyronine/reverse-triiodothyronine ratios may help obtain a more accurate evaluation of tissue thyroid status and may be useful to predict those who may respond favorably to triiodothyronine supplementation.[212,222,223,225,232]

The inaccuracy of thyrotropin and thyroxine levels in this potentially large group of individuals, including those with chronic physiologic stress, illness, and advancing age, has potentially profound implications. Studies that do not address the complex interactions of the aging thyroid and illness and use thyrotropin and thyroxine levels alone to determine thyroid status may be significantly flawed. With increasing knowledge of the complexities of thyroid function at the cellular level, it is becoming increasingly clear that the thyrotropin may not be as reliable a marker of tissue thyroid levels as once thought, especially with chronic physiologic stress, illness, inflammation, and aging. It is possible that many symptomatic patients with low tissue levels of active thyroid but normal thyrotropin and thyroxine levels would benefit from thyroid replacement both short and long term. Increasing evidence shows that thyroxine is not an optimal treatment for conditions associated with diminished use of thyroxine. Conversion of thyroxine to triiodothyronine (increased formation of reverse triiodothyronine) should lead the clinician to consider treatment with triiodothyronine.

Thyroid Preparations

Thyroid preparations include triiodothyronine (Cytomel); thyroxine (Synthroid, Levothyroxine); combinations of triiodothyronine, thyroxine; and compounded thyroid formulations (including thyroxine/triiodothyronine and timed-released triiodothyronine preparations).

Further studies are needed regarding the use of triiodothyronine preparations in the aging population and long-term outcomes based on treatment strategies that use improved methods for determining tissue thyroid levels instead of sole reliance on thyrotropin testing. With so much potential for inaccuracy in our present standard thyroid testing, the importance of additional or alternative methods for clinical assessment cannot be overemphasized. New methods of determining tissue levels of thyroid in the aging patient must be developed and used to better assess both short-term and long-term treatment effects and to help the primary practitioner assess tissue thyroid activity in the aging patient with symptoms and normal thyrotropin, thyroxine, and triiodothyronine levels.

SUMMARY

In summary, we believe the well-informed use of hormones in wellness and disease prevention will result in symptomatic improvement and should be considered an integral part in the armamentarium of options we offer our patients. Definitions and testing of hormone deficiency that apply to illnesses do not apply to wellness and prevention and need to be reevaluated while we develop new treatment paradigms to best care for our patients. With the limited amount of research focused primarily on the areas of wellness and prevention, we must acknowledge the infinite number of variables that confound the results of every study. Ultimately we must focus on the individual patient and his or her need and that is the area where the doctor–patient relationship is of utmost importance and is the key to true prevention and wellness.

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The Bioidentical Hormone Debate: Are Bioidentical Hormones (Estradiol, Estriol, and Progesterone) Safer or More Efficacious than Commonly Used Synthetic Versions in Hormone Replacement Therapy?

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Abstract

Background: The use of bioidentical hormones, including progesterone, estradiol, and estriol, in hormone replacement therapy (HRT) has sparked intense debate. Of special concern is their relative safety compared with traditional synthetic and animal-derived versions, such as conjugated equine estrogens (CEE), medroxyprogesterone acetate (MPA), and other synthetic progestins. Proponents for bioidentical hormones claim that they are safer than comparable synthetic and nonhuman versions of HRT. Yet according to the US Food and Drug Administration and The Endocrine Society, there is little or no evidence to support claims that bioidentical hormones are safer or more effective. **Objective:** This paper aimed to evaluate the evidence comparing bioidentical hormones, including progesterone, estradiol, and estriol, with the commonly used nonbioidentical versions of HRT for clinical efficacy, physiologic actions on breast tissue, and risks for breast cancer and cardiovascular disease. **Methods:** Published papers were identified from PubMed/MEDLINE, Google Scholar, and Cochrane databases, which included keywords associated with bioidentical hormones, synthetic hormones, and HRT. Papers that compared the effects of bioidentical and synthetic hormones, including clinical outcomes and in vitro results, were selected. **Results:** Patients report greater satisfaction with HRTs that contain progesterone compared with those that contain a synthetic progestin. Bioidentical hormones have some distinctly different, potentially opposite, physiological effects compared with their synthetic counterparts, which have different chemical structures. Both physiological and clinical data have indicated that progesterone is associated with a diminished risk for breast cancer, compared with the increased risk associated with synthetic progestins. Estriol has some unique physiological effects, which differentiate it from estradiol, estrone, and CEE. Estriol would be expected to carry less risk for breast cancer, although no randomized controlled trials have been documented. Synthetic progestins have a variety of negative cardiovascular effects, which may be avoided with progesterone. **Conclusion:** Physiological data and clinical outcomes demonstrate that bioidentical hormones are associated with lower risks, including the risk of breast cancer and cardiovascular disease, and are more efficacious than their synthetic and animal-derived counterparts. Until evidence is found to the contrary, bioidentical hormones remain the preferred method of HRT. Further randomized controlled trials are needed to delineate these differences more clearly.

Keywords: bioidentical hormones; synthetic hormones; hormone replacement therapy; estriol; progesterone; conjugated equine estrogens; medroxyprogesterone acetate; breast cancer; cardiovascular disease

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Introduction

The relative safety of bioidentical hormone replacement compared with traditional synthetic and animal-derived versions, such as conjugated equine estrogens (CEE), medroxyprogesterone acetate (MPA), and other synthetic progestins is the subject of intense debate. According to The Endocrine Society Position Statement, there is little or no evidence to support the claim that bioidentical hormones are safer or more effective than the commonly used synthetic versions of hormone replacement therapy (HRT).[1] Furthermore, the US Food and Drug Administration (FDA) has ordered pharmacies to stop providing estriol, stating that it is a new, unapproved drug with unknown safety and effectiveness.

Nevertheless, estriol has been used for decades without reported safety concerns and is a component of medications approved for use worldwide. The FDA has acknowledged that it is unaware of any adverse events associated with the use of compounded medications containing estriol, and US Congress is considering a resolution (HR342) to reverse the FDA's decision to restrict its use. Claims by The Endocrine Society and the FDA are in direct contrast to those of proponents of bioidentical hormones, who argue that these hormones are safer than comparable synthetic versions of HRT. Such claims are not fully supported, which can be confusing for patients and physicians.

One major reason for a lack of conclusive data is that, until recently, progestogens were lumped together because of a commonly held belief that different forms of progestogens would have identical physiological effects and risks, because they all mediate effects via the same (progesterone) receptor. This view also applies to the different forms of estrogen, which are commonly grouped together and referred to as estrogen replacement therapy.

The term "bioidentical HRT" refers to the use of hormones that are exact copies of endogenous human hormones, including estriol, estradiol, and progesterone, as opposed to synthetic versions with different chemical structures or nonhuman versions, such as CEE. Bioidentical hormones are also often referred to as "natural hormones," which can be confusing because bioidentical hormones are synthesized, while some estrogens from a natural source, such as equine urine, are not considered bioidentical because many of their components are foreign to the human body.

This review will examine the differences between the bioidentical hormones estriol, estradiol, and progesterone when used as components of HRT compared with synthetic or nonidentical hormones such as CEE and synthetic progestins, including MPA. The article attempts to determine whether there is any supporting evidence that bioidentical hormones are a potentially safer or more effective form of HRT than the commonly used synthetic versions.

Methods

Definitions

Bioidentical hormones have a chemical structure identical to human hormones but are chemically synthesized, such as progesterone, estriol, and estradiol. Nonbioidentical hormones are not structurally identical to human hormones and may either be chemically synthesized, such as MPA, or derived from a nonhuman source, such as CEE.

Databases and Keywords

Literature searches were conducted for HRT formularies, focusing on those that either are or have been used in the United States. Published papers identified for review by PubMed/MEDLINE, Google Scholar, and Cochrane database searches included the keywords: "bioidentical hormones," "synthetic hormones," "progestin," "menopausal hormone replacement," "hormone replacement therapy," "HRT," "estriol," "progesterone," "natural hormones," "conjugated equine estrogens," "medroxyprogesterone acetate," "breast cancer," and "cardiovascular disease."

Comparisons

Published papers that focused on 3 key areas were identified: 1) clinical efficacy, 2) physiologic actions on breast tissue, and 3) risks for breast cancer and cardiovascular disease. Papers included human clinical studies that compared bioidentical and nonbioidentical hormones, animal studies based on similar comparisons, and in vitro experimental work that focused on physiological or biochemical aspects of the hormones.

Results

1) Symptomatic Efficacy of Synthetic Progestins versus Progesterone

Four studies of patients using HRT, including either progesterone or MPA, compared efficacy, patient satisfaction, and quality of life. Women in all 4 studies reported greater satisfaction, fewer side effects, and improved quality of life when they were switched from synthetic progestins to progesterone replacement.[2–6] In a cross-sectional survey, Fitzpatrick et al compared patient satisfaction and quality of life, as well as other somatic and psychological symptoms (ie, anxiety, depression, sleep problems, menstrual bleeding,

vasomotor symptoms, cognitive difficulties, attraction, and sexual functioning) in 176 menopausal women on HRT with MPA versus HRT with progesterone.[2] Significant differences were seen for all somatic, vasomotor, and psychological symptoms, except for attraction, when bioidentical progesterone was used rather than MPA ($P < 0.001$).

The effect of progesterone compared with MPA included a 30% reduction in sleep problems, a 50% reduction in anxiety, a 60% reduction in depression, a 30% reduction in somatic symptoms, a 25% reduction in menstrual bleeding, a 40% reduction in cognitive difficulties, and a 30% improvement in sexual function. Overall, 65% of women felt that HRT combined with progesterone was better than the HRT combined with MPA.[2]

In a randomized study comparing HRT with MPA or progesterone in 23 postmenopausal women with no mood disorders such as depression or anxiety, Cummings and Brizendine found significantly more negative somatic effects but no differences in mood assessment with synthetic hormones. These negative effects included increased vaginal bleeding ($P = 0.003$) and increased breast tenderness ($P = 0.02$), with a trend for increased hot flashes with the use of MPA compared with progesterone.[3] In the 3-year, double-blind, placebo-controlled Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, 875 menopausal women received either placebo, CEE with MPA (cyclic or continuous), or progesterone (cyclic). Those taking progesterone had fewer episodes of excessive bleeding than those on MPA (either continuous or cyclic),[4] but no differences were noted in symptomatic relief.[5]

2) Differing Physiological Effects of Bioidentical Progesterone and Synthetic Progestins

Progesterone and synthetic progestins generally have indistinguishable effects on endometrial tissue, which are not the focus of this review. Studies that compared the physiological differences in breast tissue of those on progesterone, with those on other progestins, have the potential to predict differing risks of breast cancer. While variations in methodology and study design are considerable, most of the literature demonstrates physiological differences between progestins and progesterone and their effects on breast tissue.

Synthetic progestins have potential antiapoptotic effects and may significantly increase estrogen-stimulated breast cell mitotic activity and proliferation.[7–21] In contrast, progesterone inhibits estrogen-stimulated breast epithelial cells.[16,22–28] Progesterone also downregulates estrogen receptor-1 (ER-1) in the breast,[27–29] induces breast cancer cell apoptosis,[30,31] diminishes breast cell mitotic activity,[7,16,22–24,26–28,31,32] and arrests human breast cancer cells in the G1 phase by upregulating cyclin-dependent kinase inhibitors and downregulating cyclin D1.[23,32]

Synthetic progestins, in contrast, upregulate cyclin D1[21] and increase breast cell proliferation.[7–21] Progesterone consistently demonstrates antiestrogenic activity in breast tissue.[7,16,22,24–29,31–34] This result is generally in contrast to that for synthetic progestins, especially the 19-nortestosterone-derived progestins, which bind to estrogen receptors in breast tissue (but not in endometrial tissue) and display significant intrinsic estrogenic properties in breast but not endometrial tissue.[11,23,35–39]

Synthetic progestins may also increase the conversion of weaker endogenous estrogens into more potent estrogens,[7,40–45] potentially contributing to their carcinogenic effects, which are not apparent with progesterone. Synthetic progestins may promote the formation of the genotoxic estrogen metabolite 16-hydroxyestrone.[41] Synthetic progestins, especially MPA, stimulate the conversion of inactive estrone sulfate into active estrone by stimulating sulfatase,[43,44] as well as increasing 17-beta-hydroxysteroid reductase activity,[7,40,42,43,45] which in turn increases the intracellular formation of more potent estrogens and potentially increases breast cancer risk. Progesterone has an opposite effect, stimulating the oxidative isoform of 17-beta-hydroxysteroid dehydrogenase, which increases the intracellular conversion of potent estrogens to their less potent counterparts.[34,46,47]

At least 3 subclasses of progesterone receptors (PR) have been identified: PRA, PRB, and PRC, each with different cellular activities.[48–52] In normal human breast tissue, the ratio of PRA:PRB is approximately 1:1.[50,53] This ratio is altered in a large percentage of breast cancer cells and is a risk for breast cancer.[50,53,54] In contrast to progesterone, synthetic progestins alter the normal PRA:PRB ratio,[55–57] which may be a mechanism by which synthetic progestins increase the risk for breast cancer.

Synthetic progestins and progesterone have a number of differences in their molecular and pharmacological effects on breast tissue, as some of the procarcinogenic effects of synthetic progestins contrast with the anticarcinogenic properties of progesterone.[8,16,22,24–26,31,33,40,58–70]

3) Breast Cancer and Cardiovascular Disease Risks

Risk for Breast Cancer with Synthetic Progestins

Many studies have assessed the risk for breast cancer with the use of a synthetic progestin for HRT. Despite significant variability in study design, synthetic progestins have been clearly associated with an increased risk for breast cancer.[7,8,58,71–98]

The Women's Health Initiative (WHI), a large randomized clinical trial, demonstrated that a synthetic progestin, MPA, as a component of HRT significantly increased the risk for breast cancer (relative risk [RR] = 1.26, 95% confidence interval [CI]: 1.00–1.59).[71–74] This trial confirmed results from numerous other groups demonstrating that a synthetic progestin significantly increases breast cancer risk.[7,75–98] In addition, higher doses of progestins, testosterone-derived synthetic progestins, and progestin-only regimens further increase the risk for breast cancer.[8,75–77,80,91] The Nurses' Health Study, which followed 58 000 postmenopausal women for 16 years (725 000 person-years), found that, compared with women who never used hormones, use of unopposed postmenopausal estrogen from ages 50 to 60 years increased the risk for breast cancer to age 70 years by 23% (95% CI: 6–42). The addition of a synthetic progestin to the estrogen replacement resulted in a tripling of the risk for breast cancer (67% increased risk) (95% CI: 18–136).[98]

Ross et al compared the risk for breast cancer in 1897 women on combined estrogen and synthetic progestin with 1637 control patients who had never used HRT. Synthetic progestin use increased the risk for breast cancer by approximately 25% for each 5 years of use compared with estrogen alone (RR = 1.25, 95% CI: 1.02–1.18).[82] In a meta-analysis of 61 studies, Lee et al found a consistently increased risk for breast cancer with synthetic HRT, with an average increase of 7.6% per year of use (95% CI: 1.070–1.082), and also found that higher doses of synthetic progestins conferred a significantly increased risk for breast cancer.[75] Ewertz et al examined the risk for breast cancer for approximately 80 000 women aged 40 to 67 years from 1989 to 2002. For women older than 50 years, current use of synthetic HRT increased the risk for breast cancer by 61% (95% CI: 1.38–1.88). Longer duration of use and the use of synthetic progestins derived from testosterone were associated with increased risk.[76] Newcomb et al studied the risk for breast cancer with synthetic HRT (80% used CEE and 86% used MPA) in more than 5000 postmenopausal women aged 50 to 79 years. They found a significant increase in breast cancer of 2% per year for the estrogen-only group (RR = 1.02/yr, 95% CI: 1.01–1.03/yr), and a 4% increase per year if a synthetic progestin was used in addition to the estrogen (RR = 1.04/yr, 95% CI: 1.01–1.08/yr). Higher doses of progestin increased the risk for breast cancer, and use of a progestin-only preparation doubled the risk for breast cancer (RR = 2.09, 95% CI: 1.07–4.07).[77]

Risk for Breast Cancer with Bioidentical Progesterone

Progesterone and synthetic progestins have generally indistinguishable effects on endometrial tissue. However, as discussed above, there is significant evidence that progesterone and synthetic progestins have differing effects on breast tissue proliferation. Thus, progesterone and synthetic progestins would be expected to carry different risks for breast cancer. Although no randomized, controlled trials were identified that directly compared the risks for breast cancer between progesterone and synthetic progestins, large-scale observational trials[58,59] and randomized placebo control primate trials[16] do show significant differences. Furthermore, in contrast to the demonstrated increased risk for breast cancer with synthetic progestins,[7,8,58,71–98] studies have consistently shown a decreased risk for breast cancer with progesterone.[22,23,25,60,61,66–70,99–101]

In 2007, Fournier et al reported an association between various forms of HRT and the incidence of breast cancer in more than 80 000 postmenopausal women who were followed for more than 8 postmenopausal years.[59] Compared with women who had never used any HRT, women who used estrogen only (various preparations) had a nonsignificant increase of 1.29 times the risk for breast cancer ($P = 0.73$). If a synthetic progestin was used in combination with estrogen, the risk for breast cancer increased significantly to 1.69 times that for control subjects ($P = 0.01$). However, for women who used progesterone in combination with estrogen, the increased risk for breast cancer was eliminated with a significant reduction in breast cancer risk compared with synthetic progestin use ($P = 0.001$).[59]

In a previous analysis of more than 50 000 postmenopausal women in the E3N-EPIC cohort, Fournier et al found that the risk for breast cancer was significantly increased if synthetic progestins were used (RR = 1.4), but was reduced if progesterone was used (RR = 0.9). There was a significant difference in the risk for breast cancer between the use of estrogens combined with synthetic progestins versus estrogens combined with progesterone ($P < 0.001$).[58]

Wood et al investigated whether the increased breast cancer risk with synthetic progestins was also seen when

progesterone was used.[16] Postmenopausal primates were given placebo, estradiol, estradiol and MPA, and estradiol and bioidentical progesterone, with each treatment for 2 months with a 1-month washout period. Ki67 expression is a biomarker for lobular and ductal epithelial proliferation in the postmenopausal breast and is an important prognostic indicator in human breast cancer.[102] Compared with placebo, significantly increased proliferation was found with the combination of estrogen and MPA in both lobular ($P = 0.009$) and ductal ($P = 0.006$) tissue, but was not seen with the combination of estrogen and progesterone. Intramammary gene expressions of the proliferation markers Ki67 and cyclin B1 were also higher after treatment with estrogen and MPA (4.9-fold increase, $P = 0.007$ and 4.3-fold increase, $P = 0.002$, respectively) but not with estrogen and progesterone. Inoh et al investigated the protective effect of progesterone and tamoxifen on estrogen- and diethylstilbestrol-induced breast cancer in rats. The induction rate, multiplicity, and size of estrogen-induced mammary tumors were significantly reduced by simultaneous administration of either tamoxifen or progesterone.[25]

Chang et al examined the effects of estrogen and progesterone on women prior to breast surgery in a double-blind, placebo-controlled study in which patients were given placebo, estrogen, transdermal progesterone, or estrogen and transdermal progesterone for 10 to 13 days before breast surgery. Estrogen increased cell proliferation rates by 230% ($P < 0.05$), but progesterone decreased cell proliferation rates by 400% ($P < 0.05$). Progesterone, when given with estradiol, inhibited the estrogen-induced breast cell proliferation.[22] Similarly, in a randomized, double-blind study, Foidart et al also showed that progesterone eliminated estrogen-induced breast cell proliferation ($P = 0.001$).[23]

A prospective epidemiological study demonstrated a protective role for progesterone against breast cancer.[99] In this study, 1083 women who had been treated for infertility were followed for 13 to 33 years. The premenopausal risk for breast cancer was 5.4 times higher in women who had low progesterone levels compared with those with normal levels (95% CI: 1.1–49). The result was significant, despite the fact that the high progesterone group had significantly more risk factors for breast cancer than the low progesterone group, highlighting the importance of this parameter. Moreover, there were 10 times as many deaths from cancer in the low progesterone group compared with those with normal progesterone levels (95% CI: 1.3–422).[99] Women with low progesterone have significantly worse breast cancer survival rates than those with more optimal progesterone levels.[100,101]

In a prospective study, luteal phase progesterone levels in 5963 women were measured and compared with subsequent risk for breast cancer. Progesterone was inversely associated with breast cancer risk for the highest versus lowest tertile (RR = 0.40, 95% CI: 0.15–1.08, P for trend = 0.077). This trend became significant in women with regular menses, which allowed for more accurate timing of collection (RR = 0.12, 95% CI: 0.03–0.52, $P = 0.005$).[61] Other case-control studies also found such a relationship.[66–70]

Peck et al conducted a nested case-control study to examine third-trimester progesterone levels and maternal risk of breast cancer in women who were pregnant between 1959 and 1966. Cases (n = 194) were diagnosed with in situ or invasive breast cancer between 1969 and 1991. Controls (n = 374) were matched to cases by age at the time of index pregnancy using randomized recruitment. Increasing progesterone levels were associated with a decreased risk of breast cancer. Relative to those with progesterone levels in the lowest quartile (< 124.25 ng/mL), those in the highest quartile (> 269.97 ng/mL) had a 50% reduction in the incidence of breast cancer (RR = 0.49, CI 0.22–1.1, P for trend = 0.08). The association was stronger for cancers diagnosed at or before age 50 years (RR = 0.3, CI: 0.1–0.9, P for trend = 0.04).[60] Preeclampsia, with its associated increased progesterone levels, is also associated with a reduced risk for breast cancer.[103–105]

Estriol and the Risk for Breast Cancer

Estrogen effects are mediated through 2 different estrogen receptors: estrogen receptor-alpha (ER-α) and estrogen receptor-beta (ER-β).[106–111] Estrogen receptor-α promotes breast cell proliferation, while ER-β inhibits proliferation and prevents breast cancer development via G2 cell cycle arrest.[106,112–117]

Estradiol equally activates ER-α and ER-β, while estrone selectively activates ER-α at a ratio of 5:1.[118,119] In contrast, estriol selectively binds ER-β at a ratio of 3:1.[118,119] This unique property of estriol, in contrast to the selective ER-α binding by other estrogens,[107,118–121] imparts to estriol a potential for breast cancer prevention,[59,122–125] while other estrogens would be expected to promote breast cancer.[106,112–115,126] As well as selectively binding ER-α, CEE components are potent downregulators of ER-β receptors.[114] Whether this activity is unique to CEE is unclear, but it could potentially increase carcinogenic properties.

Furthermore, synthetic progestins synergistically downregulate ER-β receptors,[114] a possible mechanism underlying

the breast-cancer-promoting effect of CEE in conjunction with synthetic progestins. Conjugated equine estrogens also contains at least one particularly potent carcinogenic estrogen, 4-hydroxy-equilenin, which promotes cancer by inducing DNA damage.[127–131]

Because of its differing effects on ER-α and ER-β, we would expect that estriol would be less likely to induce proliferative changes in breast tissue and to be associated with a reduced risk of breast cancer.[40,59,80,103–105,122–125,132–144] Only one in vitro study on an estrogen receptor-positive breast cancer tissue cell line demonstrated a stimulatory effect of estriol as well as for estrone and estradiol.[145] Melamed et al demonstrated that, when administered with estradiol, estriol may have a unique ability to protect breast tissue from excessive estrogen-mediated stimulation. Acting alone, estriol is a weak estrogen, but when given with estradiol, it functions as an antiestrogen. Interestingly, estriol competitively inhibits estradiol binding and also inhibits activated receptor binding to estrogen response elements, which limits transcription.[135] Patentable estriol-like selective estrogen receptors modulators (SERMs) are being developed to prevent and treat breast cancer.[106,112,113,115]

Estriol and progesterone levels dramatically increase during pregnancy (an approximate 15-fold increase in progesterone and a 1000-fold increase in estriol), and postpartum women continue to produce higher levels of estriol than nulliparous women.[136] This increased exposure to progesterone and estriol during and after pregnancy confers a significant long-term reduction in the risk for breast cancer.[40,103–105,136–141] If these substances were carcinogenic, it would be expected that pregnancy would increase the risk for breast cancer rather than protect against it. Urinary estriol levels in postmenopausal women show an inverse correlation with the risk for breast cancer in many,[125,132–134,142,143,146] but not all, studies.[147]

Lemon et al demonstrated that estriol and/or tamoxifen, as opposed to other estrogens, prevented the development of breast cancer in rats after the administration of carcinogens.[123,124] Mueck et al compared the proliferative effects of different estrogens on human breast cancer cells when combined with progesterone or synthetic progestins.[24] They found that progesterone inhibited breast cancer cell proliferation at higher estrogen levels, but that synthetic progestins had the potential to stimulate breast cancer cell proliferation when combined with the synthetic estrogens equilin or 17-alpha-dihydroequilin, which are major components of CEE. This demonstrates a mechanism for the particularly marked increased risk for breast cancer when CEE is combined with a synthetic progestin.

In a large study of more than 30 000 women by Bakken et al, the use of estrogen-only HRT increased the risk of breast cancer compared with that in nonusers (RR = 1.8, 95% CI: 1.1–2.9). The addition of a synthetic progestin further increased breast cancer risk (RR = 2.5, 95% CI: 1.9–3.2) while the use of an estriol-containing preparation was not associated with the risk of breast cancer that was seen with other preparations (RR =1.0, 95% CI: 0.4–2.5).[144]

In a large case-control study of 3345 women aged 50 to 74 years, the use of estrogen only, estrogen and synthetic progestin, or progestin only was associated with a significantly increased risk of breast cancer (RR = 1.94, 95% CI: 1.47–2.55; RR = 1.63, CI: 1.37–1.94; and RR = 1.59, CI: 1.05–2.41, respectively). The risk of breast cancer among estriol users was, however, not appreciably different than among nonusers (RR = 1.10, CI: 0.95–1.29).[80] Large-scale randomized control trials are needed to quantify the effects of estriol in the risk of breast cancer.

Cardiovascular Risk with Synthetic Progestins versus Progesterone

The WHI study demonstrated that the addition of MPA to Premarin® (a CEE) resulted in a substantial increase in the risk of heart attack and stroke.[71–73] This outcome with MPA is not surprising because synthetic progestins produce negative cardiovascular effects and negate the cardioprotective effects of estrogen.[71,73,148–172] Progesterone, in contrast, has the opposite effect because it maintains and augments the cardioprotective effects of estrogen, thus decreasing the risk for heart attack and stroke.[148–151,153,155,157,162,165,167,173–178]

One mechanism contributing to these opposing effects for cardiovascular risk is the differing effects on lipids. Medroxyprogesterone acetate and other synthetic progestins generally negate the positive lipid effects of estrogen and show a consistent reduction in HDL,[148,153–159,163] the most important readily measured determinant of cardioprotection, while progesterone either maintains or augments estrogen's positive lipid and HDL effects.[148,154,155,157,173,176] For instance, the PEPI trial, a long-term randomized trial of HRT, compared a variety of cardiovascular effects including lipid effects of both MPA and progesterone in combination with CEE. While all regimens were associated with clinically significant improvements in lipoprotein levels, many of estrogen's beneficial effects on HDL-C were negated with the addition of MPA. The addition of progesterone to CEE, however, was associated with significantly higher HDL-C levels than with MPA and CEE (a notable sparing of estrogen's beneficial effects) ($P < 0.004$).[154]

Fahraeus et al compared the lipid effects of synthetic progestins with progesterone in 26 postmenopausal women who had been receiving cutaneous estradiol for 3 to 6 months. Women received either 120 μg of l-norgestrel or 300 mg of progesterone sequentially for another 6 months. Compared with the use of progesterone, l-norgestrel resulted in significant reductions in HDL and HDL-2 ($P < 0.05$).[155]

Ottosson et al compared the lipid effects of estrogen when combined with either of 2 synthetic progestins, or bioidentical progesterone.[148] Menopausal women were initially treated with 2 mg estradiol valerate (cyclical) for 3 cycles, and then were randomized to receive MPA, levonorgestrel, or progesterone. Serum lipids and lipoproteins were analyzed during the last days of the third, fourth, and sixth cycles. Those receiving estrogen combined with levonorgestrel had a significant reduction in HDL and HDL subfraction 2 (18% and 28%, respectively; $P < 0.01$), as did those receiving MPA (8% and 17%, respectively; $P < 0.01$). Conversely, there were no significant changes seen in the HDL and HDL subfraction levels with the use of progesterone.[148] Furthermore, a randomized trial by Saarikoski et al which compared the lipid effects in women using the synthetic progestin norethisterone and progesterone, those on synthetic progestin had a significant decrease in HDL, whereas those using progesterone had no decrease in HDL ($P < 0.001$).[153]

A number of studies have shown that coronary artery spasm, which increases the risk for heart attack and stroke, is reduced with the use of estrogen and/or progesterone.[149–151-,174,179,180] However, the addition of MPA to estrogen has the opposite effect, resulting in vasoconstriction,[149–151,174] thus increasing the risk for ischemic heart disease. Minshall et al compared coronary hyperreactivity by infusing a thromboxane A2 mimetic in primates, which were administered estradiol along with MPA or progesterone. When estradiol was given with progesterone, the coronary arteries were protected against induced spasm. However, the protective effect was lost when MPA was used instead of progesterone.[149]

Miyagawa et al also compared the reactivity of coronary arteries in primates pretreated with estradiol combined with either progesterone or MPA. None of the animals treated with bioidentical progesterone experienced vasospasm, while all of those treated with MPA showed significant vasospasm.[151] Mishra et al[150] also found that progesterone protected against coronary hyperreactivity, while MPA had the opposite effect and induced coronary constriction.

In a blinded, randomized, crossover study, the effects of estrogen and progesterone were compared with estrogen and MPA on exercise-induced myocardial ischemia in postmenopausal women with coronary artery disease. Women were treated with estradiol for 4 weeks and then randomized to receive either progesterone or MPA along with estradiol. After 10 days on the combined treatment, the patients underwent a treadmill test. Patients were then crossed over to the opposite treatment, and the treadmill exercise was repeated. Exercise time to myocardial ischemia was significantly increased in the progesterone group compared with the MPA group ($P < 0.001$).[162]

Adams et al[152,175] examined the cardioprotective effects of CEE and progesterone versus CEE and MPA in primates fed atherogenic diets for 30 months. The CEE and progesterone combination resulted in a 50% reduction in atherosclerotic plaques in the coronary arteries ($P < 0.05$).[175] This result was independent of changes in lipid concentrations. However, when MPA was combined with the CEE, almost all the cardioprotective effect (atherosclerotic plaque reduction) was reversed ($P < 0.05$).[152] Other studies have shown that progesterone by itself,[167,177,181] or in combination with estrogen,[152,175,177] inhibits atherosclerotic plaque formation. Synthetic progestins, in contrast, have a completely opposite effect: they promote atherosclerotic plaque formation and prevent the plaque-inhibiting and lipid-lowering actions of estrogen.[152,164,166]

Transdermal estradiol, when given with or without oral progesterone, has no detrimental effects on coagulation and no observed increased risk for venous thromboembolism (VTE).[161,182–184] This result is in contrast to an increased risk for VTE with CEE, with or without synthetic progestin, which significantly increases the risk for VTE, whether both are given orally (eg, oral estrogen and oral synthetic progestin),[71,73,160,171] as transdermal estrogen and oral synthetic progestin,[161] or both estrogen and synthetic progestin given transdermally.[185,186] Canonico et al compared the risk for VTE with different forms of HRT in 271 cases and 610 controls. They found that transdermal estradiol and oral progesterone or pregnane derivatives (progestins derived from progesterone) were not associated with VTE risk (RR = 0.7; 95% CI: 0.3–1.9 and RR = 0.9; 95% CI: 0.4–2.3, respectively). In contrast, the use of nonpregnane derivatives increased VTE risk 4-fold (RR = 3.9; 95% CI: 1.5–10).[161]

Medroxyprogesterone acetate also has undesirable intrinsic glucocorticoid activity,[187,188] whereas progesterone does not have such negative effects and is a competitive inhibitor of aldosterone, which is generally a desirable effect.[189] No changes in blood pressure are observed with progesterone in normotensive postmenopausal women, but a slight reduction in blood pressure is shown in hypertensive women.[190,191]

Synthetic progestins can significantly increase insulin resistance,[167–170,191] when compared with estrogen and progesterone.[169,170,191]

The expression of vascular cell adhesion molecule-1 (VCAM-1) is one of the earliest events in the atherogenic process. Otsuki et al compared the effects of progesterone and MPA on VCAM-1 expression and found that progesterone inhibited VCAM-1. No such effect was observed with MPA ($P < 0.001$).[165]

Discussion

Physicians must translate both basic science results and clinical outcomes to decide on the safest, most efficacious treatment for patients. Evidence-based medicine involves the synthesis of all available data when comparing therapeutic options for patients. Evidence-based medicine does not mean that data should be ignored until a randomized control trial of a particular size and duration is completed. Rather, it demands an assessment of the current available data to decide which therapies are likely to carry the greatest benefits and the lowest risks for patients.

Progesterone, compared with MPA, is associated with greater efficacy, patient satisfaction, and quality of life. More importantly, molecular differences between synthetic progestins and progesterone result in differences in their pharmacological effects on breast tissue. Some of the procarcinogenic effects of synthetic progestins contrast with the anticarcinogenic properties of progesterone, which result in disparate clinical effects on the risk of breast cancer. Progesterone has an antiproliferative, antiestrogenic effect on both the endometrium and breast tissue, while synthetic progestins have antiproliferative, antiestrogenic effects on endometrial tissue, but often have a proliferative estrogenic effect on breast tissue. Synthetic progestins show increased estrogen-induced breast tissue proliferation and a risk for breast cancer, whereas progesterone inhibits breast tissue proliferation and reduces the risk for breast cancer.

Until recently, estriol was available in the United States as a compounded prescription, but was banned in January 2008 by the FDA, which stated that it was a new, unapproved drug with unknown safety and effectiveness, although its symptomatic efficacy is generally not in question.[192–196] The FDA has not received a single report of an adverse event in more than 30 years of estriol use. Estriol is also the subject of a US Pharmacopeia monograph. The FDA Modernization Act of 1997 clearly indicated that drugs with a US Pharmacopeia monograph could be compounded. It appears that the FDA took action, not because estriol is at least as safe and effective as current estrogens on the market, but in response to what was considered unsupported claims that estriol was safer than current forms of estrogen replacement and because there is no standardized dose. Estriol has unique physiologic properties associated with a reduction in the risk of breast cancer, and combining estriol with estradiol in hormone replacement preparations would be expected to decrease the risk for breast cancer.

In cardiovascular disease, synthetic progestins, as opposed to progesterone, negate the beneficial lipid and vascular effects of estrogen. Transdermal bioidentical estrogen and progesterone are associated with beneficial cardiovascular and metabolic effects compared with the use of CEE and synthetic progestins.

Based on both physiological results and clinical outcomes, current evidence demonstrates that bioidentical hormones are associated with lower risks than their nonbioidentical counterparts. Until there is evidence to the contrary, current evidence dictates that bioidentical hormones are the preferred method of HRT.

Conclusion

A thorough review of the medical literature supports the claim that bioidentical hormones have some distinctly different, often opposite, physiological effects to those of their synthetic counterparts. With respect to the risk for breast cancer, heart disease, heart attack, and stroke, substantial scientific and medical evidence demonstrates that bioidentical hormones are safer and more efficacious forms of HRT than commonly used synthetic versions. More randomized control trials of substantial size and length will be needed to further delineate these differences.

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Conflict of Interest Statement

Kent Holtorf, MD discloses no conflicts of interest.

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PERSONAL PERSPECTIVE

Percutaneous administration of progesterone: blood levels and endometrial protection

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ABSTRACT

There is controversy about the beneficial effects of topical progesterone creams used by postmenopausal women. A major concern is that serum progesterone levels achieved with progesterone creams are too low to have a secretory effect on the endometrium. However, antiproliferative effects on the endometrium have been demonstrated with progesterone creams when circulating levels of progesterone are low. Thus, effects of topical progesterone creams on the endometrium should not be based on serum progesterone levels, but on histologic examination of the endometrium. Despite the low serum progesterone levels achieved with the creams, salivary progesterone levels are very high, indicating that progesterone levels in serum do not necessarily reflect those in tissues. The mechanism by which the serum progesterone levels remain low is not known. However, one explanation is that after absorption through the skin, the lipophilic ingredients of creams, including progesterone, may have a preference for saturating the fatty layer below the dermis. Because there appears to be rapid uptake and release of steroids by red blood cells passing through capillaries, these cells may play an important role in transporting progesterone to salivary glands and other tissues. In contrast to progesterone creams, progesterone gels are water-soluble and appear to enter the microcirculation rapidly, thus giving rise to elevated serum progesterone levels with progesterone doses comparable to those used in creams.

Key Words: Progesterone cream – Progesterone gel – Endometrium – Serum progesterone levels – Postmenopausal women – Skin.

The recent editorial by Dr. Gambrell[1] and accompanying article by Wren et al[2] in the January–February 2003 issue of *Menopause* has generated considerable controversy about the clinical effectiveness of topical progesterone creams in postmenopausal women. In his editorial, Dr. Gambrell discussed several studies using those creams. He concluded that, although progesterone in creams can be absorbed through the skin, low serum progesterone levels are achieved, with limited symptom relief. Dr. Gambrell also pointed out that none of the studies revealed any improvement in parameters such as endometrial protection, bone mineral density, or cardiovascular markers.

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CHARACTERISTICS AND ABSORPTION OF PROGESTERONE CREAMS

Topical creams consist of a variety of lipid-soluble ingredients with different characteristics. The ingredients include agents that penetrate, moisturize, and lubricate the skin, and/or act as emulsifiers. Topical progesterone creams contain a blend of those agents with progesterone, which is also lipophilic. After topical administration of a progesterone cream, the lipophilic substances in the cream, including progesterone, undergo absorption by passive diffusion

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through the different layers of the skin and its appendages. Thereafter, a resorption process occurs by which progesterone enters the cutaneous microcirculation and eventually the systemic circulation.

A number of factors can influence the percutaneous absorption of a drug, eg, progesterone, from a vehicle such as a cream[3-5]; they include progesterone concentration, physical and chemical properties of ingredients in the cream, solubility of progesterone in the cream, the extent to which the cream ingredients can change the integrity of the skin, and the site and surface area of cream application. Because progesterone creams can vary widely with respect to the types and characteristics of ingredients that they contain, and their site of application, the extent of progesterone absorption will also vary widely. The importance of differences in percutaneous progesterone absorption at different sites of application in women is evident in a study by Krause et al.[6] They showed a significant increase in serum progesterone levels 30 to 120 minutes after applying a progesterone ointment on the breast, but no increase was observed after application of the same ointment on other regions (thigh, abdomen).

CIRCULATING PROGESTERONE LEVELS ACHIEVED WITH PROGESTERONE CREAMS

One of the most important beneficial effects of progesterone creams should be the protection of the endometrium in postmenopausal women using estrogen treatment. However, a major concern in studies of topical progesterone creams is that serum or plasma progesterone levels achieved with these formulations are too low to have an antiproliferative effect on the endometrium. In a study by Burry et al,[7] six postmenopausal women applied the topical cream, Pro-Gest (Transitions For Health, Inc., Portland, OR), containing 30 mg progesterone, on the arms, legs, or chest daily for 2 weeks and then twice daily for another 2 weeks. During the progesterone treatment, the women were also treated daily with 50 μg estradiol administered transdermally by patch. The patch was changed twice weekly. Blood samples were obtained at 0, 1, 2, 3, 4, 6, 8, 12, and 24 hours on days 1, 8, 15, 22, and 29. After treatment, serum progesterone levels increased significantly from baseline values ($<$ 0.2 ng/mL) and peak levels were obtained at variable times in all subjects. Average progesterone concentrations measured in serum samples obtained at each of the 8 sampling times on the 5 days of frequent sampling ranged from 1.0 to 3.3 ng/mL. In a similar study performed by Carey et al,[8] 24 postmenopausal women were randomized to apply progesterone cream (Progestelle, Natural Medicine Company, Burwash, UK) to a specific area of the medial aspect of the dominant forearm, using a progesterone dose of 40 mg once daily or 20 mg twice daily for a duration of 6 weeks. Blood was obtained at 0, 2, 4, 6, 12, and 24 hours on days 1 and 42 of treatment. No significant difference was observed in serum progesterone levels between the once and twice daily dosage regimens. Calculated mean values for the peak progesterone concentration (C_{max}) and area under the progesterone concentration-time curve from 0 to 24 hours ($AUC_{0\text{-}24h}$) in the combined groups were 0.22 ng/mL and 1.48 ng·h·mL^{-1}, respectively, on day 1 of treatment. These values increased to 1.67 ng/mL and 16.4 ng·h·mL^{-1}, respectively, on treatment day 42. Urinary pregnanediol glucuronide, the major metabolite of progesterone in urine, was also quantified in this study. Although its levels were shown to increase after progesterone treatment, they remained in the follicular phase range.

In the studies by Burry et al[7] and Carey et al,[8] as well as other studies,[9-14] of topical progesterone cream administered to postmenopausal women, the average serum progesterone levels did not exceed 3.5 ng/mL (Table 1). The progesterone doses used in those studies did not exceed 80 mg per day.

EFFECT OF PROGESTERONE CREAMS ON THE ENDOMETRIUM

It is a widely held assumption that serum progesterone levels greater than 5 ng/mL must be achieved to inhibit endometrial mitosis and to induce a secretory change. This threshold level is based on the observation that during a normal menstrual cycle, the corpus luteum produces circulating progesterone levels that are in the range of approximately 5 to 20 ng/mL. Wren et al[10] showed no evidence of a secretory endometrium in postmenopausal women using a topical cream (Pro-Feme Cream, Lawley Pharmaceuticals, Perth, Australia) containing 16, 32, or 64 mg of progesterone, which was administered daily for 14 continuous days (days 15-28) in each of three 28-day cycles, during which a weekly 0.05 mg transdermal estradiol patch was used. Endometrial biopsies were taken pretreatment on day 14 of cycle 1 and during treatment on days 27 or 28 of cycle 3.

Although serum progesterone levels ($<$ 3.5 ng/mL) found in studies of topical progesterone creams are generally considered too low to cause a secretory endometrium (Table 1), two reports contradict this generality. In one of the studies, Leonetti et al[13] randomly placed postmenopausal women on either a 0% (control, N = 10), 1.5% (15 mg, N = 11), or 4.0% (40 mg, N = 11)

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TABLE 1. *Summary of studies showing circulating progesterone (P) levels and effects on endometrium, after administration of topical P cream in postmenopausal women*

Study	No. of subjects	Type of cream	Daily P dose (mg)	Duration of treatment (wks)	Mean P levels[a] (ng/mL)	Effect on endometrium
Burry et al[7]	6	Pro-Gest	30 and 30 × 2[b]	2 for each dose	3.3	ND[c]
Carey et al[8]	24[d]	Progestelle	40 or 20 × 2	6	1.67	ND
Copper et al[9]	10	Pro-Gest	40-80	1.4	2.9	ND
Wren et al [10,11]	27[d]	Pro-Feme	16, 32 or 64	2 in each of 3 cycles	<3.5	Not secretory
Lewis et al[12]	24[d]	Compounded	0, 40 or 80	6[e]	3.5	ND
Leonetti et al[13]	37[d]	Pro-Gest	0, 15 × 2, or 40 × 2	4	low[f]	Antiproliferative
Landes et al[14]	40	Pro-Gest	20	24	Not given	Atrophic in 28

[a]Maximum levels achieved in serum or plasma.
[b]×2 indicates twice daily treatment.
[c]Not determined.
[d]Randomized to treatment groups.
[e]A progesterone-free week was included after the first 3 weeks.
[f]Actual values not stated.

dose of the topical progesterone cream, Pro-Gest, which was administered twice daily (total daily dose 0, 30, and 80 mg, respectively). The cream was used in conjunction with an oral 0.625 mg dose of conjugated equine estrogens (CEE) daily for 28 days. Biopsies were obtained at pretreatment and on day 28 of progesterone treatment. They were reviewed blindly by two pathologists using numerical endometrial proliferation scores (EPS) from 0 (inactive) to 4 (highly proliferative). The results show that the scores decreased significantly at the end of treatment (0.0-0.2), as compared to the pretreatment and placebo scores (2.1 to 2.2 and 1.8 to 1.9, respectively). Although no progesterone values were reported by the investigators, they did state that plasma progesterone concentrations were low and varied widely among individuals.

The demonstration of antiproliferative endometrium with use of topical progesterone cream is also supported by preliminary data presented by Landes et al.[14] In their study, postmenopausal women received a pretreatment endometrial biopsy and were randomized to receive either 0.625 mg of CEE and 2.5 mg of medroxyprogesterone acetate orally, or the same oral estrogen and 20 mg of progesterone in the topical cream, Pro-gest, daily for 6 months. Of the 40 women who received a posttreatment endometrial biopsy, the endometrium was atrophic in 28 subjects and proliferative in 6 subjects in each of the oral and transdermal progestin-treated groups. No information was given about serum progesterone levels in this study.

In the studies by Leonetti et al[13] and Landes et al,[14] it may very well be that the reason for not observing secretory changes in the endometrium after topical cream progesterone therapy is the low level of estradiol that is typically achieved with menopausal estrogen therapy. It has been our experience that some recipients of egg donation exhibit a lack of secretory changes on endometrial biopsy, even after 14 days of treatment with 4 mg of oral micronized estradiol daily followed by 7 days of 200 mg of vaginal progesterone given three times daily. In all of these instances, an increase in the estradiol dose in a subsequent cycle has resulted in the attainment of an appropriately secretory endometrium. Thus, the antiproliferative effect described by Leonetti et al[13] and Landes et al[14] may be all that can be observed at the low levels of estradiol priming, and may very well correlate with the avoidance of endometrial hyperplasia.

Although several factors can be proposed to explain why antiproliferative endometrium was not found in the study by Wren et al,[10] one possible deficiency in their study appears to be the short duration of progesterone treatment during each cycle. In their study, the investigators used the Pro-Feme Cream, manufactured by Lawley Pharmaceuticals (Perth, Australia). The product information sheet that accompanies the cream contains the following statement: "In general most significant physiologic results are not experienced by patients until the fourth to sixth week of usage." Because the women in the study by Wren et al[10] applied the cream topically for only 2 weeks of each cycle, the duration of treatment may not have been sufficient to cause a biologic effect on the endometrium. This is important because it is well recognized that, with respect to endometrial protection, length of progestin treatment is more important than dose.

DISCREPANCY BETWEEN SERUM AND TISSUE LEVELS OF PROGESTERONE

The demonstration by Leonetti et al[13] and Landes et al[14] that topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium when circulating progesterone levels are low indicates

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that the endometrial progesterone concentrations were sufficiently high enough to produce a biologic effect in most of the study subjects. These findings are consistent with data from other studies, which show that circulating levels of a steroid may not reflect its concentration in a particular tissue. In one of our studies,[15] we found a conspicuous variability between serum and secretory endometrial progesterone concentrations after vaginal or intramuscular administration of progesterone to premenopausal women. After 6 days of dosing, peak serum progesterone levels were considerably lower after vaginal administration of 200 mg progesterone every 6 hours compared to intramuscular injection of 50 mg progesterone twice daily (11.9 vs 69.8 ng/mL, respectively). Endometrial concentrations of progesterone, however, were significantly greater after vaginal administration than after intramuscular administration (11.5 vs 1.4 ng/g protein, respectively). Our results were subsequently confirmed by Cicinelli et al[16] in a study similar to ours, except that endometrial tissue specimens were obtained from hysterectomy specimens. The findings in the two studies not only demonstrate that serum progesterone levels may not reflect progesterone levels in a particular tissue, but also lend support to the hypothesis that there is preferential distribution of vaginally administered progesterone to the uterus ("first uterine pass effect").[17,18]

In another study by Cicinelli et al,[19] the investigators showed a marginal increase in mean serum progesterone levels from baseline to end of treatment (0.6 to 3.9 ng/mL), following repetitive administration of a nasal progesterone spray during the last 10 days of a 1 month cycle in which 8 postmenopausal women ingested CEE daily. However, histologic examination of the endometrium in each subject showed secretory changes at the end of treatment from the proliferative state observed at baseline.

Additional evidence demonstrating that progesterone levels in serum may not reflect those measured in tissues is found in studies showing that progesterone levels in saliva are very high after topical progesterone cream application, even though serum progesterone levels are low.[11,12,20] O'Leary et al[20] measured progesterone in saliva samples obtained at 0, 0.5, 1, 2, 4, 16, and 24 hours after a single application of a cream containing 64 mg of progesterone (Pro-Feme Cream) on an inner arm of each of 6 postmenopausal women. Mean salivary progesterone levels were found to increase from baseline levels of 0.09 ng/mL to peak values of 18 ng/mL at 1 hour after treatment, but serum progesterone levels did not change significantly. The salivary progesterone levels fell to baseline values by 24 hours. It is now well recognized that salivary progesterone levels can increase from baseline levels by at least two orders of magnitude after topical cream application, depending on dose and time of saliva sampling. These findings are consistent with rapid uptake of progesterone by salivary glands. Presumably there is also rapid uptake of progesterone by other tissues, eg, the endometrium, after topical cream administration; however, this has not yet been demonstrated.

TRANSPORT OF STEROIDS BY RED BLOOD CELLS

It has been proposed that red blood cells may play an important role in transporting progesterone to salivary glands and other tissues throughout the body. The binding of steroids to red blood cells was first demonstrated in 1969.[21] More recently, Koefoed and Brahm[22] studied the in vitro release rates of several ^{3}H-labeled sex steroids, including progesterone, from human red blood cells. Their results showed that as much as 15% to 35% of the total hormone content in whole blood may be confined to red blood cells. These findings are compatible with a model of rapid transition of hormone through the red blood cell membrane and intracellular binding. The authors concluded that the release of steroid hormones from red blood cells is a very fast process, and that these cells may be regarded as transporters of steroid hormones in a manner similar to that of albumin, which has a low affinity but high capacity for steroid hormones.

When progesterone cream is applied to skin, the red blood cells passing through capillaries in that skin are exposed to very high concentrations of progesterone. Because the transit time of red blood cells from capillaries has been shown to be very rapid ($\approx$1 s),[22] progesterone may be delivered directly to tissues via red cells without having a chance to equilibrate with the systemic blood. In the study by Lewis et al[12] that showed high salivary progesterone levels in conjunction with low levels of progesterone in plasma after treatment with a topical progesterone cream (Pharmaceutical Compounding NZ Ltd., Auckland, New Zealand) in postmenopausal women, the investigators also quantified progesterone in red blood cells from these subjects. The subjects were randomized to receive one of three different progesterone doses: 0 (placebo), 20, or 40 mg. Treatment was performed daily for 3 weeks, followed by a treatment-free week and an additional 3 weeks of treatment. Blood samples were obtained at 0, 1, 3, 4, 7, and 8 weeks after treatment. The results show that after progesterone treatment there was large intersubject variability in red blood cell progesterone

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levels, which did not exceed 0.27 ng/mL (vs 1.1 and 25.8 ng/mL in plasma and saliva, respectively). The highest increases (23% and 45%) in red blood cell progesterone levels in each treatment group were observed after 1 week. Although the investigators of that study concluded that the progesterone levels in red blood cells were too low to be important in the delivery of progesterone to target tissues, it should be realized that even small amounts of progesterone taken up by red blood cells might be important because the transit time of red blood cells from capillaries is very rapid. The traditional view is that albumin, SHBG, and CBG are the important transporters of steroid hormones. However, the role of red blood cells in steroid hormone transport has not been studied thoroughly, and such studies are warranted.

PROGESTERONE GELS

Although progesterone levels in salivary glands are high after topical progesterone cream application, the concomitant low progesterone levels found in serum may best be explained by the characteristics of progesterone creams. In our preliminary study[23,24] with a progesterone gel, we found that serum progesterone levels increased by 50% to 100% from baseline levels and remained in the follicular phase range (< 0.5 ng/mL) after administration of a 30-mg progesterone dose. However, with 100-mg progesterone doses, peak serum progesterone levels of 5.9 to 8.0 ng/mL were found at 2 to 3 hours after dosing, and thereafter, similar levels were achieved at 1, 2, and 4 weeks of treatment.

No studies have been performed in which direct comparisons of absorption rates were made between progesterone creams and gels. However, it appears that steroidal compounds are generally absorbed better from gels. One possible explanation for this is that after absorption through the skin the lipophilic ingredients of creams, which include progesterone, may have a preference for saturating the fatty layer below the dermis instead of resorption into the cutaneous microcirculation. Because topical progesterone creams contain relatively high doses of the steroid (16- to 80-mg doses have been studied), even a small portion of the dose entering the microcirculation in the skin could account for the high salivary progesterone concentrations found soon after application of the cream. In contrast to progesterone creams, progesterone gels are generally prepared by dissolving the steroid in alcohol, and mixing the alcoholic solution with hydroxypropyl methylcellulose and water. This mixture is water-soluble and appears to enter the microcirculation rapidly after its absorption through the skin.

METABOLISM OF PROGESTERONE BY SKIN

It has been suggested that because transdermally delivered progesterone is a substrate for 5α-reductase in skin,[25] conversion of progesterone to 5α-reduced metabolites may be a significant factor contributing to low serum progesterone levels and urinary pregnanediol glucuronide excretion. However, one would expect to find low serum progesterone levels after topical administration not only of creams but also of gels containing progesterone. Our study[23,24] showed that elevated serum progesterone levels are obtained with progesterone gel administration. In the study by Lewis et al[12] described earlier, the investigators also concluded that conversion of progesterone by 5α-reductase is an unlikely mechanism to account for low systemic progesterone levels. They found that serum progesterone levels and urinary pregnanediol glucuronide excretion were not increased after treatment of a single subject with the 5α-reductase inhibitor, finasteride.

CONCLUSIONS

It is obvious that long-term randomized, placebo-controlled trials are required to demonstrate the beneficial effects of topical progesterone creams conclusively. Studies investigating the effect of topical cream on the endometrium should not be based on serum progesterone levels but on histologic examination of the endometrium. Also, conclusions cannot be made about potential beneficial effects of topical progesterone creams on other parameters, such as vasomotor symptoms, urogenital atrophy, bone mineral density, cardiovascular markers, cognitive function, and mood, until a wide range of progesterone doses, eg, 50, 100, and 150 mg, and different formulations of progesterone creams are investigated. Finally, an alternate approach that should be considered is the use of a progesterone gel instead of a progesterone cream for studying beneficial effects of progesterone on the endometrium and other parameters. Progesterone gels are rapidly absorbed, show a dose response of progesterone, and yield relatively high levels of serum progesterone. The argument that therapeutic creams are preferred over gels by postmenopausal women for cosmetic reasons will be weakened if the progesterone gel is shown to be more reliable and clinically more effective than the cream.

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