Alternatives to Estrogen for Menopausal Women (44203)

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Abstract. **Limited acceptable alternatives to hormone replacement therapy exist for use by postmenopausal women. This oversight within the biomedical community is of particular concern considering the increasing number of postmenopausal women and the current low use of hormone replacement therapy. In addition, contraindications to hormone replacement therapy and controversies regarding recommendations for use of hormone replacement therapy also exist. With the notable exception of the advances in prevention of osteoporosis, alternatives to estrogen for other aspects of the sequelae of hypoestrogenism or aging are limited. Furthermore, there is widespread use of complementary therapies among postmenopausal women despite a lack of data on efficacy or safety of such therapies. Increased research into alternatives to estrogen for menopausal women is of clinical, scientific, and health policy importance.** [P.S.E.B.M. 1998, Vol 217]

Alternatives to estrogen and hormone replacement therapy (HRT; estrogen plus progestin) are needed for use by menopausal women. This need is highlighted by the current low use of HRT and the projected need for HRT and alternatives in the future. Furthermore, controversies regarding the use of HRT are likely to continue for at least the next decade. The controversies surrounding the use of HRT exist at many levels ranging from the need for medical therapy of a normal physiologic process to uncertainties regarding the magnitude of benefits and risks associated with HRT. The low use of HRT by women (in the range of 10%–35%) is related in part to side effects and awareness of the controversies within the biomedical community. Alternatives to estrogen have been consistently used by women, often supported by health care providers and promoted by the lay press. Alternatives to estrogen can be roughly divided into new drug development (e.g., multiple therapies approved or in testing for treatment of osteoporosis), and non-drug therapies. Non-pharmacologic therapies include life-style changes as well as a number of "complementary therapies" such as herbal therapies that are widely used but only recently receiving attention by the scientific community. In this review, the current status of both pharmacologic and nonpharmacologic alternatives to estrogen will be addressed.

Hormone Replacement Therapy

Prevalence of Use. Over the past four decades the relative popularity of hormone replacement therapy use by menopausal women has fluctuated significantly. In the early 1970s, estrogen therapy was very popular, with use declining in the mid 1970s mid reports of increased uterine cancer with unopposed estrogen use, and a resurrection of use in the 1980s–1990s due to apparent benefits of osteoporosis prevention and reduction in the risk of coronary artery disease. Currently in the United States, hormone replacement therapy remains one of the most commonly prescribed medications, with 31.7 million prescriptions dispensed in 1992 (1). However, of the 40 million U.S. women eligible for HRT, most women do not use it. A recent poll revealed a 34% current use of HRT in women aged 45–60; however, in many regions of the United States, as well as subpopulations of women, HRT use is substantially lower (10%–15%) (2, 3). Furthermore, with the aging of the "baby boomers," an additional 20 million women will soon become eligible for HRT. The low use of HRT is related to a number of factors. About 10% of postmenopausal women have contraindications to estrogen use. Some women may not be using HRT due to lack of access to health care and appropriate counseling regarding risks and benefits. However, the majority of women not using HRT appear to be bothered by side effects and concerned about a possible increase in breast cancer risk.

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U.S. Recommendations. The United States Preventive Services Task Force recommends that health care providers discuss the risks and benefits of HRT with menopausal women (4). A recommendation is not made that all women should or should not take HRT, and it is stated that there is insufficient evidence to make such a recommendation. Furthermore, it is emphasized that women should fully participate in the decision, and that the decision should be individualized. Counseling women regarding HRT should include an evaluation of the impact of menopausal symptoms as well as risk for heart disease, osteoporosis, and breast cancer. Lastly, it is recommended that women are counseled regarding available alternatives to hormones for menopause management.

Controversies Regarding the Use of HRT. Controversies regarding HRT include questions regarding the need for medical therapy of a natural physiologic process and controversies regarding the magnitude of relative risks and benefits, particularly with long-term use of HRT. Estrogen benefits include relief of vasomotor symptoms (hot flushes and night sweats) and vaginal atrophic changes (5, 6). Long-term apparent benefits of estrogen include reduction in risk of osteoporosis and coronary artery disease (7, 8). Preliminary evidence also suggests a reduction in risk for colon cancer and development of Alzheimer's disease with estrogen use (9, 10). Risks of estrogen therapy include an increase in uterine cancer (this risk is largely negated by the addition of progestins), a possible increase in thromboembolic phenomena, increased risk of gallbladder disease, and a possible increase in the risk of breast cancer (11, 12, 13). Contraindications to estrogen use include undiagnosed abnormal uterine bleeding, past history of an estrogen dependent malignancy, active liver disease, active thromboembolic disease, or a past history associated with estrogen use. These contraindications are likely to be modified over the ensuing decades. An example is changing U.S. policy on re-evaluating risk-benefit ratios of HRT in women with a past history of breast cancer.

Many of the controversies surrounding use of HRT persist because a large prospective placebo-controlled clinical trial of HRT has *not* been undertaken. Therefore, current risk-benefit ratios are based on epidemiologic observational studies. Observational studies raise the possibility of selection bias and do not prove a causal relationship (14). These epidemiological studies indicate that HRT use results in about a 37% decrease in relative risk for death (15). This is attributable primarily to a reduction in cardiovascular disease deaths. There was an attenuation of the benefits of HRT use with long-term use (greater than 10 years) due to an increase in breast cancer mortality. Computer modeling studies, assuming a 40% reduction in relative risk for coronary disease, a 54% reduction in hip fracture risk, and a 30% increase in breast cancer risk, also indicate that most American women would extend life expectancy with the use of HRT (16). However, controversies remain in the absence of a clinical trial. The United States is now conducting a large randomized, double-blind, placebo-controlled trial of HRT (the Women's Health Initiative) that will address many of these issues. Worldwide, there are four ongoing clinical trials of HRT with heart disease as a major endpoint.

Vasomotor Symptoms

Vasomotor symptoms are experienced by up to 85% of menopausal women in Western countries (5). Interestingly, this is not true worldwide, with many countries and cultures reporting a much lower prevalence of hot flushes. Although the physiology of vasomotor instability has not been fully elucidated, the hot flush is associated in changes in skin conductance, heart rate, core temperature, and a coincident pulse of LH. Hot flashes can be experienced as an insignificant problem by women. Conversely, significant hot flushes, and particularly night sweats, can be disruptive and result in chronic sleep disturbance. Many symptoms previously attributed to menopause (fatigue, irritability, short-term memory loss) may be secondary to chronic sleep deprivation. Estrogens are very effective therapy and can reduce hot flushes by up to 90%. Alternatives to estrogen include hormonal and nonhormonal therapies with varying degrees of efficacy and side effects.

Hormonal Therapies. Synthetic progestins have been well-documented to reduce hot flushes and in some studies match the efficacy of estrogens. Medroxyprogesterone acetate has been found to reduce vasomotor symptoms. In a direct comparison of 150 mg of intramuscular medroxyprogesterone acetate versus conjugated estrogens, the reduction in hot flushes was nearly identical (17). Oral medroxyprogesterone acetate at a dose of 20 mg/day has been shown to reduce hot flushes by 74% in a placebo controlled trial (18). More recently, a study was conducted with megestrol acetate in women with a past history of breast cancer. Results demonstrated an 85% reduction in hot flushes (19). Adrogens have been studied in a limited way for hot flushes, with danocrine found to reduce hot flushes in a subset of women in a randomized double-blind study (20). Testosterone and synthetic derivatives are often combined with estrogen. Testosterone does not inhibit the efficacy of estrogen with regard to relief of hot flushes. Tibolone (Org-OD14) is a synthetic steroid with estrogenic, progestational, and androgenic activity and has been shown to have a beneficial effect on hot flashes (21).

Concerns with the use of these hormonal therapies for vasomotor symptoms relate to side effects and lack of data in women with a past history of breast cancer. Synthetic progestins may cause irregular uterine bleeding, adverse mood changes, and lower HDL levels. Androgens also decrease HDL levels. For all of the steroidal compounds, long-term safety in women with a past history of breast cancer has not been established.

Nonhormonal Agents. Clonidine is an alpha-adrenergic receptor agonist used for hypertension. Several studies have demonstrated the efficacy of clonidine on both subjectively and objectively measured hot flashes in post-

menopausal women. Unfortunately the side effect profile of clonidine including fatigue, irritability, headache, nausea, and dizziness results in significant compliance problems (22). A study of transdermal clonidine administration found that 80% of women reported a reduction in hot flushes with fewer side effects (23). Methyldopa may also be effective in reduction of symptoms of hot flushes (24). Bellergal is a compound containing phenobarbital, belladonna, and ergotamine with mixed data supporting a reduction in hot flushes. Bellergal is not a treatment of choice, as this multidrug compound has a number of contraindications and more potential for drug-drug interactions, and phenobarbital has addictive potential.

Nonpharmacologic Approaches. Nonpharmacologic approaches to hot flush reduction have not been well-studied. Environmental ambient temperature can influence hot flush frequency and intensity; therefore, modifying ambient temperature can be helpful (5). Anecdotally, women describe various triggers to hot flushes that could be modified. These include various foods, caffeine, and alcohol. The effect of exercise on hot flush frequency is undergoing investigation. Further investigative efforts with regard to complementary therapies, including herbal therapies and acupuncture, will be discussed below. Behavioral therapies have been studied and are effective in hot flush reduction. Central sympathetic activation is increased in women with hot flushes, and behavioral relaxation methods reduce sympathetic activity in normal subjects, prompting investigation of the effect of behavioral therapies on hot flush reduction. An example is the 40% reduction in objectively measured hot flushes with paced respirations as described by Freedman and Woodward (25).

Urogenital Target Tissues

The effect of hypoestrogenism on urogenital target tissues is predominantly related to vaginal dryness, vaginal pH changes, and superficial dyspareunia (6). The relative impact of hypoestrogenism versus aging on bladder function is less well established. Estrogens are highly effective in relieving vaginal symptoms. Nonestrogen treatments for vaginal symptoms have been limited. Water soluble lubricants ranging from KY-Jelly to Astroglide can provide some symptomatic relief; however, they have no significant effect on changes of vaginal pH, grams of secretion, or maturational index of vaginal cytology. Vaginal moisturizers, and in particular a new mucoadherent compound, polycarbophil, are an alternative to conventional lubricants. These compounds adhere to the vaginal mucosa and are hygroscopic. There has been some ability of these agents to lower vaginal pH, and in one clinical trial 61.5% of the patients preferred the polycarbophil-based product with 26.5% preferring a water-based lubricant and 12% having no preference (26). Sexual activity decreases vaginal atrophy as measured by turgor, elasticity and vaginal depth (27). Regular sexual activity also maintains a lower vaginal pH. Vaginal administration of estrogen is generally well absorbed into the circulation; therefore, this therapy has met resistance with regard to use in women with contraindications to estrogen. Recently, a vaginal ring that releases 17β-estradiol at a rate of 7.5 μg/day has been approved for vaginal atrophy. Excluding the first 24 hours, the plasma circulating levels of estradiol remain in the untreated postmenopausal range with this estradiol vaginal ring, and endometrial stimulation does not occur (28). Therefore, this may be an acceptable treatment for vaginal atrophy, even for those women with contraindications to estrogen.

Bladder symptoms include both stress- and urge-type incontinence. Although estrogens appear subjectively to improve incontinence symptoms, particularly urgency, objective demonstration has been mixed. Pelvic floor exercise programs may be used as an alternative to estrogen for incontinence symptoms. These exercises may be enhanced by both pelvic floor electrical stimulation and by biofeedback. In patients requiring additional therapies, urodynamic testing will provide the direction of therapy that may be surgical (stress incontinence) or pharmacologic (urge incontinence).

Osteoporosis

Alternatives to hormone replacement therapy are more advanced with regard to osteoporosis prevention and treatment than any other menopausal endpoint. Skeletal bone mass increases through childhood, and peak bone mass, lower in women than in men, is achieved near the age of 30. There is an age-related decline in bone mass beginning in mid-life, and an acceleration of bone loss associated with menopause in women. Therefore, postmenopausal women, are at particular risk for development of osteoporosis. Low bone density correlates strongly with increased risk for fracture, including vertebral, Colles, and hip fractures. The largest cause of morbidity and mortality is related to hip fractures. Currently hip fractures occur in about 250,000 women per year in the United States at a cost of about $10 billion annually (29). The devastating effects of hip fractures include a substantial excess mortality following fracture, resulting in 40,000 deaths annually, and the morbidity of loss of mobility and chronic pain. The mainstay of osteoporosis prevention is adequate calcium intake, exercise, and estrogen therapy. Estrogen prevents loss of bone density, and epidemiologic studies suggest a 50%–60% reduction in fractures (30). Rapid advances in research related to the treatment and prevention of osteoporosis have now led to breakthroughs in nonestrogenic therapies.

Preventive Care. It is suggested that preventive care should begin in adolescence, as during this period bone mass is in the growth phase. Although peak bone mass is primarily genetically determined, adequate exercise, calcium, and diet in the adolescent years should allow maximization of the genetic potential for peak bone mass. Studies of calcium supplementation in adolescents are ongoing (31). The effect of calcium intake on fracture in postmenopausal women is not clear; however, there is a general

agreement that total elemental calcium of 1000–1500 mg/day is an adequate intake for postmenopausal women, and in many cases not achieved by diet alone (32). Vitamin D is recommended at doses of 400–800 units/day, with higher doses often indicated in the elderly. Weight-bearing exercise for at least 30 minutes at least 3 times/week has numerous benefits including preservation of bone mineral density, as well as better muscular tone and stability that may reduce the propensity to fall (33, 34).

Nonestrogenic Hormonal Therapies. Tibolone is a synthetic steroid with estrogenic, progestational, and androgenic activity. It does not result in endometrial stimulation and is used as a single agent therapy for menopausal symptoms (35). Several studies have now evaluated bone protective effects of Tibolone. In a 2-year study, tibolone has been demonstrated to increase bone mass 2.5% at the lumbar spine and 3.5% at the femoral neck compared to losses of 2.9% and 3.7% respectively in placebo (36). Tibolone is approved in many European countries and is currently undergoing multi-center trials in the United States. Long-term effects on breast cancer incidence and cardiovascular mortality are unknown.

Tamoxifen is a triphenylethylene antiestrogen with mixed estrogen agonist/antagonist activities that are tissue and species specific. Tamoxifen is widely used in women diagnosed with breast cancer and is undergoing evaluation in a breast cancer prevention trial. Excluding the impact on the breast, tamoxifen has apparent antiestrogen effects in the brain (induction of hot flushes), and estrogenic effects on bone, lipids, and endometrium. In postmenopausal women, tamoxifen increased lumber spine bone density by 1.4%, with a loss of 0.7% in the placebo (37). In addition, tamoxifen has a beneficial effect in decreasing cholesterol and LDL, and one study has demonstrated a reduction in myocardial infarction (38, 39). The experience with tamoxifen has been a model for the development of Selective Estrogen Receptor Modulators (SERMs) as discussed in an accompanying review.

Bisphosphonates. Bisphosphonates are analogues of pyrophosphate that inhibit bone resorption. Initial studies of bisphosphonates in osteoporosis treatment were those of cyclic etidronate in the treatment of established vertebral osteoporosis (40). Cyclic etidronate was instituted to avoid the development of osteomalacia with continuous use. More recently, more potent bisphosphonates have been evaluated, and alendronate has been approved for osteoporosis treatment and prevention. These newer bisphosphonates do not induce osteomalacia and are given on a continuous basis. Alendronate at a dose of 10 mg/day increases bone mineral density at the lumbar spine and femoral neck by 7.2% and 5.3% respectively in a 2-year study of 188 women (41). Several additional, larger studies of the efficacy of alendronate in preserving bone density and in preventing fracture in postmenopausal women with established osteoporosis have been reported. Treatment with alendronate over 3 years in 994 women with osteoporosis revealed a vertebral fracture rate of 3.2% in the alendronate group as opposed to 6.2% in the placebo group (42). A trial of alendronate in 2027 women with low femoral-neck bone mineral density confirmed protection against vertebral fracture and additionally revealed that the relative risk of hip fracture was reduced (0.49) by alendronate treatment (43). More recently, alendronate has been studied in early postmenopausal women and has shown efficacy similar to hormone replacement therapy in prevention of bone loss at a dose of 5 mg.

Other Bone Active Drugs. Calcitonin is a peptide hormone that inhibits bone resorption by inhibiting recruitment and activity of osteoclasts. Calcitonin is not active orally; it is available as subcutaneous injection and as a nasal spray. Calcitonin increases bone mineral density especially at the spine, and some evidence exists for reduction in fracture (44). Multiple other drugs for osteoporosis prevention or treatment are under investigation. Some of these include new generation bisphosphonates, calcitriol, the active metabolite of parent vitamin D3, anabolic steroids, progestins, fluoride, parathyroid hormone, growth hormone, and bone growth factors (45).

Cardiovascular Disease

The leading cause of death in postmenopausal women is cardiovascular disease resulting in 500,000 deaths per year, with about 240,000 deaths due to atherosclerotic coronary artery disease (46). The majority of the epidemiologic data suggest that estrogen replacement reduces the relative risk of coronary artery disease by 50% (47). However, there are certainly numerous modifiable risk factors separate from estrogen that can be taken advantage of in the patient who chooses not to use estrogen. These are related to health behavior modification and controlling disease processes that increase the risk of coronary artery disease.

Health Promotion and Disease Prevention

Many leading causes of death in the United States appear to be linked to a small number of personal health habits (48). With regard to coronary disease prevention in postmenopausal women, health behavior changes that would influence risk include cigarette smoking, exercise/diet, and obesity. In addition, screening and management of hyperlipidemia, hypertension, and diabetes should result in reduced coronary disease risk.

Cigarette smoking is a strong independent risk factor for cardiovascular disease in women (49). In 1985, approximately 25.3 million women smoked. Cigarette smoking increases the risk of fatal and nonfatal coronary artery disease by 2–6-fold. It is estimated that 50% of all cases of coronary artery disease in women 30–55 years of age is due to cigarette smoking. The risk for coronary artery disease is cigarette dose-dependent. Cigarette smoking is also an independent risk factor for stroke and peripheral vascular disease. Obesity, directly or indirectly, has a significant impact on cardiovascular risk. A woman that is 30% overweight is at increased risk for heart disease even in the absence of other

risk factors. Furthermore, obesity increases the risk of diabetes and hypertension and is associated with hypercholesterolemia, which in turn increases the risk of cardiovascular disease (50, 51). This is of concern in the United States as one-third of American adults are estimated to be overweight, corresponding to about 58 million people. A sedentary life style is a major risk factor for development of cardiovascular disease (52). Aerobic exercise for 30 minutes at least 3 times/week, and preferably more frequently, is recommended. Regular physical activity also is beneficial in prevention of hypertension, obesity, diabetes, and osteoporosis. Approximately 60% of women in the United States do not engage in regular physical activity (53). A recent study found an inverse relationship between level of physical activity and all-cause mortality in postmenopausal women. An overall reduced risk of death (relative risk 0.77) occurred as well as reduced risk of death specifically from cardiovascular disease (54). Dietary excess and imbalance contribute to coronary artery disease, hypertension, obesity, diabetes, and some types of cancer. Recommendations regarding a healthy diet include limiting fat and cholesterol, maintaining caloric balance, and emphasizing foods containing fiber (fruits, vegetables, grains) (55).

From a disease-screening and prevention standpoint, coronary disease is reduced by management of hypertension, diabetes, and hyperlipidemia. Elevated blood cholesterol is a major modifiable risk factor for coronary artery disease. It is estimated that a 1% increase in cholesterol increases the coronary heart disease risk by 3%. In addition, HDL-cholesterol is an inverse, independent risk factor for coronary artery disease. Cholesterol-lowering diet and medications reduce mortality in persons with established coronary artery disease, a finding that is under investigation for asymptomatic women with hypercholesterolemia (56). Hypertension, present in more than 40 million Americans, is a contributor to coronary artery disease, stroke, renal disease, and retinopathy. Treatment of hypertension reduces mortality and cardiovascular events, particularly cerebrovascular morbidity and mortality (57). Diabetes increases the risk of cardiovascular disease. The relationship between glycemic control and duration of disease with macro vascular complications is unclear. Prospective studies are ongoing and are evaluating diet and drug therapy in noninsulin-dependent diabetes (58).

Complementary Therapies, Phytoestrogens, Antioxidant Supplements

The use of "complementary" therapies is receiving increasing attention within the United States. Examples of complementary therapies include relaxation techniques, massage, herbal medicines, homeopathy, and acupuncture. Overall, 34% of respondents of a telephone interview of 1539 adults reported using at least one complementary therapy in the past year (59). Specific to menopausal symptoms, very little is known about how prevalent the use of complementary therapies is in the United States. We found a 12% use of herbal therapies in a survey of postmenopausal women (60). Of importance, is that few studies have been performed with regard to efficacy or safety. In particular, the possibility that an herbal therapy may be the administration of unopposed estrogens needs to be addressed. *In vitro* studies have demonstrated estrogen-like actions of herbs, and case reports have reported uterine bleeding with herbal therapies (61). A number of investigators are currently conducting clinical trials to assess the efficacy of herbal therapies for menopausal symptoms. Herbal therapies for osteoporosis prevention are also being investigated. Significant data do exist on mind-body relaxation techniques for reduction of vasomotor symptoms, as previously mentioned. A few studies have also demonstrated a reduction in hot flushes with the use of acupuncture (62).

Dietary factors, and particularly phytoestrogens, may influence the incidence of vasomotor symptoms. The limited evidence for this is based on the relatively low occurrence of vasomotor symptoms in cultures in which diets are very high in phytoestrogens. In Indonesia, perimenopausal women begin increasing dietary intake of a papaya rich in phytoestrogens and have only a 30% incidence of hot flushes. In Japan, a traditional Japanese diet is rich in phytoestrogens, and women there do not appear to complain of hot flushes. A recent clinical trial of a phytoestrogen-rich diet revealed an increase in sex hormone binding protein levels and decrease in hot flush scores in the dietary phytoestrogen group (63). It is also of interest that cultures with high phytoestrogen intake are cultures with lower incidences of breast cancer. Certain phytoestrogens are antiangiogenic *in vitro* and might therefore prevent metastasis (64). Furthermore, soy protein may have benefits from a cardiovascular risk reduction by lowering cholesterol levels (65). Several large studies are currently underway to evaluate the effect of soy protein on menopausal symptoms as well as plasma lipids and bone density.

Use of antioxidant supplements remains highly controversial at this time. Although there is a general consensus that Americans could improve dietary intake of fruits and vegetables (that contain antioxidants), the relative benefits of supplementation are less clear. A few reports have indicated that Vitamin E is beneficial for reduction of hot flushes. Furthermore, epidemiologic data have correlated an increased Vitamin E intake (dietary) with reduced coronary artery disease in postmenopausal women (66).

Conclusion

There are approximately 40 million women of menopausal age in the United States, and it is estimated that this number will grow to 50 million by the turn of the century. Worldwide there are more than 300 million women in this age group. Although hormone replacement therapy is widely recommended, only a small minority of eligible women receive menopausal estrogen replacement. This low use of hormone replacement therapy is due to a number of factors that are unlikely to be resolved in the near future.

These include concerns regarding breast cancer risk, side effects of HRT, and philosophies regarding the need to treat a normal physiologic process. In this light, it is important to provide alternatives to estrogen for mid-life women. Furthermore, the wide use of "complementary" therapies deserves investigation. Not only should safety and efficacy be assessed, but novel beneficial therapies may result from such investigations. Lastly, continued awareness and promotion of preventive health services relevant to issues of postmenopausal women will certainly make for a healthier population as we approach the next century.

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