Hormone Therapy of Premature Ovarian Failure
The Case for “Natural” Estrogen

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trian hormones play an important role in women’s health, providing the most reliable and convenient means of contraception and of relieving menopausal symptoms.1,2 Hormone therapy also has other benefits, eg, regulation of menstrual irregularities and relief of dysmenorrhea in menstruating women and prevention of vulvovaginal atrophy and osteoporosis/fractures in postmenopausal women. In addition, natural estrogens, principally 17β-estradiol, and natural progesterone (but not synthetic progestins) have biological effects that protect the vasculature from oxidative and inflammatory injury and prevent cardiovascular disease.3 These functions have been adduced by some to account for the 10- to 15-year delay in presentation of clinical cardiovascular disease and events in women compared with men.

In contrast to the unquestioned benefits of endogenous ovarian hormones, hormone therapy of women with ovarian failure, whether naturally occurring or surgically induced, continues to be a topic of active debate in the scientific and popular literature. Although observational studies have shown substantial (~50% reduction in coronary heart disease) benefit of menopausal hormone therapy (also referred to as “menopausal hormone replacement therapy” or “hormone replacement therapy”) in women who choose to take them (usually beginning treatment in the perimenopausal or early postmenopausal period), randomized, controlled trials have not confirmed a cardioprotective effect and have even shown evidence of harm. Accordingly, current guidelines do not recommend use of menopausal hormone therapy for the prevention or treatment of cardiovascular disease in women.

Important limitations of the available randomized, controlled trials are that they typically enrolled women who were >60 years of age and, thus, were ≥10 years postmenopause and that they typically used nonphysiological hormone preparations, eg, conjugated equine estrogen and the synthetic progestin medroxyprogesterone acetate. Importantly, these trials do not answer questions about the effects of menopausal hormone therapy in young women, ie, those with premature ovarian failure. Although specific guidelines for hormone management of patients under age 40 years with ovarian failure are not available in the United States, the standard of practice is that conventional menopausal hormone therapies or oral contraceptives, sometimes with testosterone added, are administered until the usual age of menopause (~51 years).

In the current issue of Hypertension, Langrish et al4 compared the cardiovascular effects of physiological (transdermal estradiol and vaginal progesterone) with standard synthetic (oral ethinylestradiol and norethisterone) menopausal hormone therapy in a small group of young women (19 to 39 years of age) with premature ovarian failure of diverse etiologies. Their major findings were highly significant: 7.3/7.4 mm Hg reductions in mean 24-hour blood pressure by ambulatory blood pressure monitoring accompanied by reduced plasma angiotensin II and serum creatinine levels with the estradiol/progesterone regimen at 12 months of treatment. These findings are consistent with previous observations that both endogenous estradiol and estradiol therapy tend to lower blood pressure.3

Observational studies of blood pressure through the menstrual cycle have demonstrated that blood pressure is lower when estradiol levels peak during the luteal phase than when they are at their nadir during the follicular phase. The rise in blood pressure seen later in life in women has been related to menopause, per se, in addition to aging, and has been attributed to estrogen withdrawal, weight gain, or a combination of these and other yet-undefined neurohumoral influences.4,5 Menopause is associated with significant increases in blood pressure in most cross-sectional and longitudinal studies. For example, a prospective study of blood pressure in premenopausal, perimenopausal, and postmenopausal women has demonstrated an age-dependent 4- to 5-mm Hg increase in systolic blood pressure and a tripling in the risk of developing hypertension in postmenopausal women over a 5-year follow-up period.5

Studies of the effects of menopausal hormone therapy on blood pressure have reported a variety of findings, including blood pressure–neutral, blood pressure–lowering, and blood pressure–elevating effects, likely attributed to differences in patient populations studied and in hormone preparations administered, as well as to methodologic differences in blood pressure measurement.5 Prospective studies in which conjugated equine estrogen with or without a progestin was administered to either healthy normotensive early postmenopausal women, as in the Postmenopausal Estrogen/Progestin Interventions Trial, or to older postmenopausal women, as in the Women’s Health Initiative, found either no change or modest increases (~1 mm Hg) in systolic blood pressure with active treatment compared with placebo treatment.1

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In contrast, consistent with the report of Langrish et al., administration of transdermal estradiol in physiological doses to healthy postmenopausal women has been shown to lower nocturnal systolic, diastolic, and mean blood pressures when compared with placebo in studies that used ambulatory blood pressure monitoring. In addition, a study of ~1400 hypertensive postmenopausal women has shown that various transdermal hormone preparations lowered blood pressure by an average of 7/9 mm Hg, a result comparable with that observed by Langrish et al. in a normotensive population with premature ovarian failure. The selective benefits of transdermal estradiol over oral conjugated estrogen on blood pressure may relate to delivery of lower, more sustained levels of circulating estrogen without a potentially proinflammatory first-pass effect in the liver.

In addition, transdermal estradiol has been shown to have hemodynamic effects that are superior to those of oral conjugated estrogen. A mechanistic study that compared 6 months of treatment with transdermal estradiol plus oral medroxyprogesterone acetate to oral conjugated equine estrogen plus the same progestin preparation in healthy postmenopausal smokers demonstrated more consistent and pronounced reductions in blood pressure, total peripheral resistance, and circulating norepinephrine levels and increases in endothelium-dependent vasodilation and vascular β-adrenergoreceptor responsiveness in the transmural estradiol group. These relationships held during both resting and stress conditions. Importantly, as discussed above, serum estrogen (estradiol and estrone) concentrations were lower and more reflective of premenopausal values during transdermal estradiol treatment compared with during conjugated equine estrogen treatment.

It is important to note that aging and prolonged hormone deprivation may attenuate the favorable hemodynamic, anti-inflammatory, neurohormonal, and vasoprotective effects of estrogen. For example, menopausal hormone therapy has been shown to alter hemodynamics (blood pressure, heart rate, cardiac output, systemic vascular resistance, and plasma norepinephrine levels) under resting and behavioral stress conditions in women who were <5 years postmenopausal but not in those >5 years postmenopausal. Hormone treatment was associated with a major reduction (~8.5 mm Hg) in blood pressure in women <5 years after menopause but had no depressor effect in those who were >5 years postmenopausal. Systemic vascular resistance and plasma norepinephrine also trended downward in response to hormone therapy only in women who were <5 years postmenopausal.

Whether the improvements in endothelial function and other determinants of vascular integrity and vascular tone observed in short-term studies translate into vasoprotection and prevention of atherosclerosis with transdermal estradiol is being tested in the ongoing Kronos Early Estrogen Prevention Study. The Kronos Early Estrogen Prevention Study is evaluating the effectiveness of transdermal estradiol compared with conjugated equine estrogen in combination with cyclic oral micronized progesterone or placebo in preventing the progression of vascular disease, as assessed by ultrasound measurement of carotid intimal-medial thickness and electron beam tomographic measurement of coronary artery calcification in women aged 42 to 56 years who are within 36 months of their final menstrual period. The placebo-controlled Early Versus Late Intervention Trial With Estradiol is testing whether oral 17β-estradiol can slow the progression of vascular disease as assessed by surrogate end points in postmenopausal women. The Early Versus Late Intervention Trial With Estradiol is randomly assigning women according to their number of years since menopause (<6 versus ≥10) to receive either oral 17β-estradiol or placebo; women with a uterus also receive vaginal progesterone gel (or placebo gel) for the last 10 days of each month. Carotid artery thickness by ultrasound is the primary end point of the trial. Surrogate end points for vascular disease will be measured in both trials in lieu of morbid and mortal cardiovascular disease events, which are rare in the perimenopausal age group. As emphasized by Langrish et al., results of these important trials will inform the appropriate selection of ovarian hormone regimens for women who require long-term treatment.

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References
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