Postmenopausal Hormone Replacement Therapy: Implications for Prolonging Life

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PROLOGUE
Hormone replacement therapy has long been advocated for protection against osteoporosis and for relief of the symptoms of menopause. Recently, research has demonstrated a 40 percent reduction in the risk of coronary heart disease (CHD) in users of estrogen replacement therapy. This effect is due to the beneficial effects estrogens have on lipoproteins as well as other physiologic changes that occur under estrogen’s influence. Estrogen therapy appears to provide protection against stroke via these same mechanisms. The impact on the risk of cardiovascular disease of adding a progestin to estrogen replacement therapy is unknown. Progestins partially negate the positive alterations in lipoproteins that occur with estrogen therapy. It is unknown what effect progestins have on the physiologic changes induced by estrogen. The major risk associated with hormone replacement therapy (HRT) is a potential increase in risk of breast cancer (25 percent) following exposure of 15 years or greater. From the currently available data, HRT should be considered in all postmenopausal women unless there is a contraindication to its use.

INTRODUCTION
Based upon a life expectancy of 80 years with menopause occurring at approximately 50 years of age, a woman will spend one third of her life in a hypoestrogenic state. Given the profound effects that ovarian dysfunction may have on health and well-being it is important to develop a clinical approach for the management of the initial and the long-term complications of the menopausal transition.

This article will differentiate between menopause and the perimenopausal interval, discuss the benefits and risks of (HRT) for treatment of menopause, as well as the changes in life expectancy associated with such therapy. In particular, HRT’s role in protecting against cardiovascular disease (CVD) will be addressed.

MENOPAUSE VERSUS PERIMENOPAUSAL INTERVAL
The fifth decade of life is often a period of significant change for women as they move out of the reproductive years. The transitional (perimenopause) menstrual pattern is characterized by long intermenstrual intervals with erratic short cycles. This irregularity is caused by inconsistent maturation of the remaining ovarian follicles resulting in both ovulatory and anovulatory cycles(1). Even though during the perimenopausal period a woman may experience many of the symptoms associated with menopause she may still become pregnant. Therefore, a treatment plan that provides

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as 6 weeks with oral therapy, yet take as long as 24 weeks with transdermal administration (4).

Stampfer et al. (7) in their report of the Nurse’s Health Study Cohort demonstrated a 40 percent reduction in the risk of ischemic heart disease in women who were currently taking estrogen (alone) as postmenopausal supplementation. Two previously published meta-analyses have reported similar reductions in risk (8,9). In addition to attributing this dramatic decrease in risk to the beneficial effects of estrogen on lipoproteins, in particular increases in HDL (10), it has been suggested that estrogen administration produces additional physiologic changes which may influence risk. These changes include an estrogen induced increase in coronary blood flow via a direct effect on vessel walls (4), increases in the local production of prostacyclin (4) (vasodilatory prostaglandin that opposes platelet aggregation), decreased serum concentrations of plasma fibrinogen (11), and prevention of the oxidation of LDL which reduces its atherogenicity (12).

The extrapolation of this data to women who are currently receiving HRT in the United States is difficult. In general, women receiving HRT, unless they have had a hysterectomy, receive both estrogen and a progestin as part of their treatment regimen. The progestin, usually medroxyprogesterone acetate (MPA), is added to protect against the well established increased risk of endometrial cancer (eight fold increase) in women with a uterus who are taking unopposed estrogen (3). Typical HRT regimens followed in the United States include: (i) unopposed daily estrogen in hysterectomized women; (ii) cyclic therapy (estrogen days 1-25, progestin days 15-25, nothing days 25-1); and (iii) daily combination of estrogen and progestin. Unfortunately, progestins have the ability to attenuate the positive estrogen induced changes in lipoproteins with greatest impact on HDL-C. The degree of attenuation depends upon the androgenicity of the progestin used (MPA - low androgenicity), the dose of both the estrogen and progestin, and the regimen followed (13). Combination therapy, both cyclic and continuous has shown variable effects on HDL. This variability appears to be dose related, with doses of MPA at 55-130 mg/month allowing greater expression of the positive estrogen effects (14). The data addressing whether or not progestins attenuate or reverse the estrogen induced physiologic changes known to protect against CHD is inconclusive (3,4).

The relationship between estrogen use and stroke is less well understood. Without hormone supplementation the lifetime probability of having a stroke and the probability of death from the stroke for a 50 year old woman are estimated to be 20 percent and eight percent respectively (3). The few studies that have looked at postmenopausal estrogen use and stroke risk have reported conflicting findings (7,15-17). The most recent data were collected as part of the National Health Epidemiologic Follow-up Study (NHEFS). This national cohort reported a 30 percent reduction in the incidence of stroke and a 60 percent reduction in stroke mortality. Protection remained despite adjustment of baseline risk factors such as age, systolic blood pressure, diabetes, smoking, etc. (18). The same mechanisms involved in the protection against CHD are believed to be involved in decreasing the risk of stroke. As is true for the data on CHD prevention, the data for stroke prevention is derived from a population that only used estrogen, making extrapolation to women in the United States difficult.

RISKS

The lifetime probability of developing cancer of the endometrium for a 50 year old woman is 2.6 percent. The risk of death from the cancer is estimated to be 0.3 percent (3). In women with a uterus, unopposed estrogen therapy has been reported to increase the risk of endometrial cancer eight fold over baseline. This risk is known to increase with increasing dosage and duration of estrogen exposure (3). Five studies have examined the effects of adding a progestin to estrogen replacement therapy and the resulting risk of endometrial cancer. Four of these studies (19-22) showed a risk similar to the risk in non-users and one (23) actually showed a significant decrease in risk as compared to baseline.

There are much published data on the risk of breast cancer and estrogen therapy. Unfortunately, much of the data are inconsistent in their conclusions. A 50 year old woman who does not take HRT has a 10 percent lifetime probability of developing breast cancer and a 3 percent probability of death as a result of the cancer (3). Short-term exposure to estrogen (<five years) appears to be associated with no increase in risk (24-26). However, following exposure of 15 years or greater, which more closely represents the exposure period of those women receiving HRT, the risk appears to be increased 25 percent over that of non-users (26). It is unclear as to the advantage or disadvantage of adding a progestin. There is some cause for concern since progesterone exposure in the luteal phase of the menstrual cycle results in increased mitotic activity in breast tissue. This is in contrast to it’s effects on endometrial tissue where it decreases mitotic activity. Therefore, progestins may increase rather than decrease the risk of breast cancer (27).

Due to the association of thromboembolic complications and the use of oral contraceptives, the risk is often felt to exist with HRT. Although a statistically insignificant increase in risk of thrombosis has been found with higher estrogen doses (i.e., 1.25 mg conjugated estrogen or it’s equivalent) it appears as though the typical estrogen doses used for HRT (i.e., 0.625 mg conjugated estrogen or it’s equivalent) are not thrombogenic in postmenopausal women (28). There are no laboratory or epidemiologic data about the effects of progestins on the coagulation system of these women. Extrapolation of data from early studies with oral contraceptives would suggest progestins may provide protection against venous thromboembolism in a dose-dependent manner (28). Postmenopausal HRT is contraindicated in women with breast cancer, abnormal uterine bleeding (possibly indicative of endometrial carcinoma), or active thrombotic disease (1).

PROJECTED CHANGES IN LIFE EXPECTANCY

Grady and colleagues in a review published in Annals of Internal Medicine, projected estimated changes in life expectancy resulting from the use of hormone replacement regimens. A summary of this data is presented in Table I (3). The predicted life extension ranges from -0.5 to +2 years depending upon concomitant risk factors. This is similar to or greater than the impact of other preventive therapies. For example, the impact of treating a 35 year old woman with
mild hypertension is estimated to be + 0.9 years and for moderate hypertension is + 1.7 years(29).

CONCLUSION

Current epidemiologic evidence strongly suggests that estrogen supplementation following menopause provides protection against CVD in women. Practitioners continue to be reluctant to commit patients to years of a therapy whose benefits have been demonstrated only in observational studies, rather than proven via the rigor of prospective clinical trials. There are on-going studies such as The Women’s Health Initiative and the National Institutes of Health’s Postmenopausal Estrogen/Progestin Intervention Trial that should provide that type of data.

On the basis of the available information and since a clinically significant positive effect on life expectancy can be predicted from the relative risk data all postmenopausal women should be considered candidates for HRT and properly educated about the risks and benefits associated with such therapy, as long as no contraindications are present.

References


Table I. Net change in life expectancy as a result of HRT for a 50-year-old white woman

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Life expectancy no HRT (yrs)</th>
<th>Net change in life expectancy with HRT</th>
<th>E+Pb</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk factors</td>
<td>82.8</td>
<td>+0.9</td>
<td>+0.1</td>
</tr>
<tr>
<td>With hysterectomy</td>
<td>82.8</td>
<td>+1.1</td>
<td>NA</td>
</tr>
<tr>
<td>With CHD</td>
<td>76.0</td>
<td>+2.1</td>
<td>+0.9</td>
</tr>
<tr>
<td>At risk for CHD</td>
<td>79.6</td>
<td>+1.5</td>
<td>+0.6</td>
</tr>
<tr>
<td>At risk for breast cancer</td>
<td>82.3</td>
<td>+0.7</td>
<td>-0.5</td>
</tr>
<tr>
<td>At risk for hip fracture</td>
<td>82.4</td>
<td>+1.0</td>
<td>+0.2</td>
</tr>
</tbody>
</table>

a Adapted from reference 3.
b Assuming the addition of a progestin to the estrogen therapy attenuates the beneficial effects on coronary heart disease by 30 percent.

Net change in life expectancy

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Life expectancy no HRT (yrs)</th>
<th>Estrogen alone</th>
<th>E+Pb</th>
</tr>
</thead>
<tbody>
<tr>
<td>At risk for hip fracture</td>
<td>82.4</td>
<td>+1.0</td>
<td>+0.2</td>
</tr>
</tbody>
</table>

From the lipid research clinics program follow-up study.” Circulation, 75, 1102-1109(1987).
