THE EFFECT OF HORMONE REPLACEMENT THERAPY IN MENOPAUSE ON CARDIOPROTECTION

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SUMMARY

Cardiovascular disease (CVD) is the leading cause of death in women, and after menopause the incidence increases rapidly. The premenopausal state and estrogen status, appear to be a prophylactic against the mortality risk from CVD. The protective effect is believed to be mediated by beneficial changes in cholesterol levels. Estrogen decreases low density lipoprotein cholesterol (LDL-C) and increases high density lipoprotein cholesterol (HDL-C). The other possible mechanism is the direct effect of estrogen on arterial intima. The type and route of estrogen used in hormone replacement therapy determines the positive and negative effect of estrogen on the cardiovascular system. Most studies show a 50% or greater reduction in CVD and related mortality with postmenopausal estrogen administration. Progestogen addition to hormone replacement, may attenuate the beneficial effects of estrogen on cholesterol. However if used in low doses progesteron may not exert this negative effect on the cardivascular system.

Key words: Estrogen, Cardiovascular disease

INTRODUCTION

Women rarely have heart disease until after menopause unless they have a major coexisting disease such as familiar hypercholestrolemia or diabetes. After menopause the incidence of cardiovascular disease accelerates rapidly. In the Framingham study for example, the combined fatal and non-fatal rates of cardiovascular disease in women aged 45 to 49 lag behind those in men by about 15 years. This lag decreases to 10 years at ages 70 to 75 and after 75 the rates are nearly equal (1). In most industrialized countries, women can expect to live more than one third of their lives in postmenopausal state. Cardiovascular disease is the leading cause of death in women and accounts for 52% of all deaths in U.S. women (2). Coronary artery disease alone effects more than two million women per year in the U.S.A. Within the first several years after natural menopause, women have no appreciably increased risk of cardiovascular disease (3). However, women who have premature menopause or oopherectomy are at substantially increased risk of cardiovascular disease. Some studies have suggested that the risk in these women is seven times increased than in women with intact ovaries (4). The risk is higher in women with premature menopause because estrogen deprivation appears earlier and more abruptly.

The premenopausal state and estrogen status, appear to be a prophylactic against the mortality risk from cardiovascular disease. The purpose of this article is to review the literature to determine the mechanism of hormonally related cardioprotection.

MECHANISMS OF ESTROGEN RELATED CARDIOPROTECTION

The Framingham data (1) revealed no substantial differences between men and women in known risk factors such as elevated blood pressure, impaired glucose tolerance, except increased total cholesterol with advancing age. Before menopause, women have lower cholesterol levels than men, but their levels start to increase with the onset of menopause, and increase to a greater extent than do cholesterol levels in aging men (5). Epidemiologic data from the Lipid Research Clinics (6) have revealed that for every 1% increase in total cholesterol results in 2% increase in the risk of myocardial infarction. The pathogenetic role of cholesterol in coronary heart disease is therefore significant.

There is still dispute as to whether the principal injury to the arterial intima that culminates in myocardial infarction is primarily of a lipid or nonlipid origin. It has been established that all cases of impending myocardial infarction involve platelet aggregation and release of growth promoting substances such as platelet derived growth factor and transforming growth factor beta (7). These chemotactic factors entrapping lipids can induce the formation of foam cells. Foam cells are lipid carrying and processing macrophages that have been activated to engulf lipid, and specifically, LDL cholesterol. Damage results because the foam cells eventually occupy the lumen

of the coronary vessel and weaken the vessel wall. Rupture of arterial wall will activate the clotting mechanism and development of a coronary thrombus will lead to myocardial infarction. Macrophages may further contribute to atherogenesis by oxidation of LDL cholesterol (8,9). The oxidant forms appear to have different receptor attachments and cannot be appropriately removed, resulting in accumulation of the cholesterol in the vessels. These features make the oxidant forms of LDL cholesterol extremely atherogenic. The LDL receptor is therefore critical for removal of cholesterol from the circulation (10). If the LDL receptors are abnormal or diminished in number, severe atherosclerosis will result. Deficiency of LDL receptor can be absolute, from genetic causes or relative, in proportion to excessive dietary cholesterol intake. Levels of LDL cholesterol significantly affect cardiovascular disease mortality; for every 11% reduction in LDL cholesterol levels there is a 19% reduction in coronary artery disease risk (11). High density lipoprotein (HDL) cholesterol plays major role in the collection of excessive cholesterol and its transport back to liver for degradation and reformation of other lipoproteins. There are several forms of HDL cholesterol, but the one that is most active in reverse cholesterol transport is HDL 2 (12). The HDL2 particles are catabolized primarily in the liver under the influence of hepatic lipase. Hepatic lipase activity decreases during estrogen treatment and increases with progestogen treatment. While estrogen shuts down hepatic lipase activity, HDL cholesterol can increase in the circulation and continue to facilitate increased cholesterol transport. In both men and women, extrapolation of these data shows a greater number of coronary vessels affected when the HDL cholesterol level is lower (13). Interestingly, increased cardiovascular risk after menopause is not result of low HDL cholesterol levels. Cross sectional data have failed to show a major change in HDL cholesterol as a function of age during menopause. However HDL cholesterol levels do decline in premenopausal women made acutely estrogen deficient or in women unergoing oopherectomy. Therefore a decline in HDL cholesterol per se do not seem to increase cardiovascular risk in menopause. The causal factor changing during menopause is total cholesterol, 70% of which is composed of LDL cholesterol. Although HDL cholesterol levels do not tend to decline by postmenopausal period, it is supposed that estrogen replacement can cause an increase in HDL cholesterol in a postmenopausal woman. It was reported that 1.6 mg/dL increase in HDL cholesterol would predict a 9.2% reduction in coronary artery disease. The actual observed reduction was 7% (14). Estrogen seems to increase local production of prostacyclin which has vasodilatory properties and anti-aggregant effects. It is well known that estrogen induces an increase in blood flow. A favorable tromboxan/prostacyclin ratio plus increased blood flow may help explain the cardioprotective effects of estrogen. It is estimated that as much as 50% of the cardioprotection by estrogen in postmenopausal women cannot be explained by estrogen induced increase in HDL cholesterol levels. This suggestion directed the investigators to assess local action of estrogen on vessels. Estrogen and progesteron receptors have been found in arterial endothelial and smooth muscle cells of several mammalian species (15). Other studies have shown that estrogen treatment in vivo or in vitro is associated with reductions in lipoprotein - induced arterial smooth muscle cell proliferation (16), inhibition of the myointimal proliferation associated with mechanical endothelial injury (17), decreased collagen and elastin production (18), increased collagen and elastin degradation (19) and increased prostacyclin production (20) by arterial smooth muscle cells. These studies indicate that vascular estrogen receptors have functional capabilities and may determine atherosclerotic response at the level of arterial intima.

ESTROGEN REPLACEMENT AND CARDIOVASCULAR DISEASE

More than 20 studies have compared the frequency of myocardial infarction or ischemic heart disease according to estrogen use (Table I). Only two (29,40) of these studies suggested increase of risk with hormone use in postmenopausal women and two others showed no risk or benefit (28,41). All other studies suggested significant protection with a risk reduction of at least 50% in most cases. The Framingham study found an elevated risk which was not statistically significant when women with angina were omitted (40). As a consequence this study involved a small number of patients and had imprecise disease end points. A subsequent reanalysis of this data showed a nonsignificant protective effect among young women but a nonsignificant adverse effect among older women (41). There is less benefit perhaps an adverse effect among women taking more than 1.25 mg of conjugated estrogen daily. Such high doses were common in Framingham study which may partly explain their discrepant results.

In the Lipid Research Clinic study (35) the relative risk of cardiovascular disease was lower in hormone using women in each age group compared with nonusing women. Henderson et al (38) also found a 50 % lower risk of heart disease in women older than 70 who were treated with estrogen, suggesting that the protection continued in the later years.

The only randomised controlled clinical trial of hormone replacement therapy and cardivascular disease reported to date did used combined cyclical estrogen progesteron therapy. In that ten years study, Nachtigal et al (21) found the relative risk of heart attack in the group treated with estrogen progestin was one third of the placebo group.

The other data that supports cardioprotective properties of estrogen replacement is from a study of Sullivan et al (42). If the women with angiographically proved CHD were taking estrogen, the overall risk of death due to CHD was reduced by 60 % when the other factors such as smoking and cholesterol levels were taken into account. If severity of coronary occlusion is assessed by angiography another aspect

of replacement can be evaluated. Women taking estrogen had chance of 60 % lower risk for having moderate or severe occlusion than did women who were not taking estrogen (43). Whether women were treated with 0.625 or 1.25 mg. conjugated estrogen there was 50 % reduction in mortality due to myocardial infarction compared with untreated women. As a result if the goal is maintanence of longevity, reduction in CVD spares 90 % of the total lives saved in estrogen replacement therapy. Prevention of CVD alone by estrogen replacement causes an overall decrease in mortality 5250 per 100.000.

All of the above epidemiologic data pertain to the use of estrogen alone. Addition of progestogen which is the major complement of estrogen replacement in gynecologically intact women should also be evaluated. Although addition of progestogen seems to attenuate the effect of estrogen onto cardiovascular risk, there is still potential benefit to maintain postmenopausal women with this regimen.

Nearly all the studies suggesting protective effects of estrogen replacement therapy relate the use of unopposed oral estrogens, and relatively small number of studies can be found to determine the effects of long term combined therapy. However, one study reported that the addition of progestogen does not exert opposite effects (45).

Reduced level of HDL 2 cholesterol is largely caused by androgenic properties of the progestogen. As a rule it is expected that the added doses of progestogen results in a fall in HDL cholesterol, and an increase in LDL cholesterol levels (46). Both C19 nortestesteron (noretindrone, norgestrel, noretindrone acetate) and C 21 derivatives share that characteristic. But medroxyprogesteron acetate (MPA) reduce HDL cholesterol only slightly at doses of 10 mg. (47). Whereas levonorgestrel is the most potent progestogen in the androgenic group, natural progesteron has no major effect on HDL 2 cholesterol.

The other negative effect of progestogens is, although this is yet primarily a theoretical concern, a negative influence on vessel wall physiology by counteracting the beneficial changes mediated by estrogen. It has been suggested that even natural progesteron prevents the marked increase in prostacyclin levels induced in human umbilical arteries by estrogen (48).

The gold standard has been well defined in discussions at an international consensus conference held in 1988 (49). In view of the potential negative impact of progestogens on cardiovascular system, imperative rules of administration of progestogens can be summarized as; prescription in the lowest possible effective doses, avoidance of use of the more androgenic compounds and sparing the women who have had a hysterectomy from progestogen.

Based on available data, the daily doses necessary for endometrial secretory transformation in most patients are as follows; MPA 5-10 mgr, noretindrone or noretindron acetate, 0.7-1.0 mgr; dl norgestrel, 150 microgr; and micronized oral progesteron 300 mgr.

Still further developments and alternative strategies are needed for the optimal estrogen replacement therapy. A new generation of progestogens has been developed; such as desogestrel and gestodene. Desogestrel which minimizes the metabolic impact when prescribed in the contraceptive pill may substitute by more androgenic compounds (50).

An alternative way for avoiding hepatic metabolism is administration of progestogen transdermally in the estrogen containing patch is currently being investigated.

The rationale for the introduction of "continuous/combined therapy"" is, production of atrophic endometrium with very small progestogen doses that achieve better lipid impact and to lessen physiological side effects. However, published data on this kind of administration are relatively sparse. Favorable lipid profile was reported from the study of Hargrove et al (51). This statement is based on a 10% fall in total cholesterol and a 50 % increase in HDL cholesterol. The other study was from Mattson et al (52) who were the first to evaluate the effects of continuous regimen. In two of the four groups (norethisteron acetate 0.5 mg and megestrol acetate 2.5 mg) the 10-15 % reduction in LDL cholesterol seen at 4 months had almost disappeared at the end of 12 month period. However, whether these changes were due to factors other than treatment is not clear (52).

As a summary there is little basis for confidence that continuous/combined therapy has a more favorable impact on lipid and lipoprotein metabolism than does sequential therapy. A large, prospective, controlled study is required to assess thorough effects of this mode of therapy on cholesterol metabolism.

TYPES OF ESTROGEN AND ORAL VERSUS TRANSDERMAL ADMINISTRATION

Traditionally, estrogens used for replacement therapy in postmenopausal women have been given orally. Transdermal administration is gaining popularity and has been accepted alternative to oral replacement therapy. Only available form of oral estrogen in Türkiye is conjugated equine estrogens. Estrogen taken orally results in the virtually direct provision of pharmacologic amounts of biologically potent estrogen to the liver. Then potency of type of estrogen determines hepatic response. Potentially harmful induction of clotting factors can result from the use of large doses of a potent estrogen such as ethinyl estradiol. Natural estrogens, including estradiol and estrone and conjugated equine estrogens have less marked effects than the major synthetic estrogens, ethinyl estradiol and DES. Mashchak et al (53) reported that the natural estrogens had no major effect on the induction of globulins, though a slightly greater effect was seen with

conjugated equine estrogens than with estrone sulfate and micronized estradiol. Ethinyl estradiol produced an effect that was more than 200 times potent. Natural oral estrogen has no deleterious effect on coagulation. Studies by Notelowitz et al (54) have confirmed that the coagulation factors such as factor VII, factor X, and antitrombin III are not altered in recipients of natural estrogen replacement. For this reason, synthetic estrogens should not be used for menopausal treatment unless the doses are extremely small.

Although the hepatic first pass effect produces undesirable conditions with regard to hepatic globulins, it is also a means of increasing HDL cholesterol. Contrary to current belief, this effect is not specific to oral administration. Estrogen via nonoral routes in sufficient doses and for a sufficient time has been found to exert a beneficial effect on lipoprotein profiles. Lobo et al (55) showed that transdermal estradiol (0.1 mg) had an effect on total cholesterol and HDL cholesterol comparable to that of subdermal pellet (50 mg) after 6 months of therapy.

Recently we have demonstrated that; transdermal route is as effective as oral estrogen replacement therapy in maintaining favorable lipid profile in women who underwent total abdominal hysterectomy and bilateral oopherectomy. (Presented in 3rd International Congress of Ob & Gyn in İzmir.)

As a conclusion: replacement therapy with estrogen alone or in combination with a progestin may be indicated at the onset of menopause or symptoms of hypoestrogenism. This is particularly important in women at high risk for developing osteoporosis. Once replacement stops, bone loss resumes. Therefore for osteoporosis prevention ERT should be continued for 10 to 15 years after menopause. However, for benefit in terms of reduction in CVD, replacement therapy appears to be indicated for the woman's lifetime. In order to determine whether or not a postmenopausal woman without contraindications should receive ERT, the physician must assess the overall risks and benefits of hormone therapy. The major problems associated with he menopause are increased CVD and osteoporotic fractures, both of which carry a high rate of morbidity and mortality. Fortunately the incidence of both CVD and osteoporotic fractures can be reduced by ERT. Estrogens do have some adverse effects, primarily an increased risk of endometrial cancer when used by a woman with an intact uterus. However the addition of progestin to the regimen reduces the incidence of endometrial cancer to levels at or below those reported in untreated women. Therefore the risk/benefit ratio is very much in favor of the use of ERT in postmenopausal women who have undergone a hysterectomy or estrogen and progestin regimen in those with an intact uterus.

Table I: Summary of Studies of Replacement of Estrogen and Cardiovascular Disease

STUDY	YEAR	POPULATION	END POINTS	RELATIVE RISK	P VALUE
Nachtigall (21)	1979	84	Fatal/Nonfatal "MI"	0.33	P>0.05
Talbot (22)	1977	64	Suddendeath	0.34	P>0.05
Ross (23)	1981	133	Fatal "CHD"	0.43	P<0.01
Szklo (24)	1984	36	Nonfatal "MI"	0.61	P>0.05
Adam (25)	1981	76	Fatal "MI"	0.65	P>0.05
Pfeffer (26)	1978	185	Fatal/nonfatal "MI"	0.68	P>0.05
Rosenberg (27)	1976	336 6730 controls	Fatal/nonfatal "MI"	0.97	P>0.05
Rosenberg (28)	1980	477 1832 controls	Nonfatal "MI"	1.00	P>0.05
Jick (29)	1978	17	Nonfatal "MI"	7.5	P>0.05
Lafferty (30)	1985	124	Fatal/nonfatal "MI"	0.16	P=0.05
Macmahan (31)	1978	1891	All "CVD"	0.30	NA
Stampfer (32)	1985	32317	All "CVD"	0.30	P<0.01
Hammond (33)	1979	610	All "CVD"	0.33	P<0.01
Potocki (34)	1971	198	All "CVD"	0.33	NA
Bush (35)	1983	2270	"CVD" mortality	0.34	P<0.05
Busch (36)	1974	737	Fatal "CHD"	0.43	P<0.05
Petit (37)	1979	16638	"CVD" deaths	0.50	P<0.05
Henderson (38)	1986	7610	Fatal/nonfatal "MI"	0.54	P<0.05
Paganini (39)	1988	8832	Fatal stroke	0.53	P<0.05
Wilson (40)	1985	1234	All "CVD"	1.76	P<0.05

Table II. Commonly Used Oral Estrogens

Preparation	Dose
Conjugated equine estrogens	0.625 to 1.25 mg
Piperazine estrogen sulfate	0.625 to 1.25 mg
Micronized 17 beta estradiol	1.0 to 2.0 mg
17 alfa ethinyl estradiol	0.01 to 0.02 mg

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