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Exercise, Nutrition, and the Coagulation Effects of Estrogen Replacement on Cardiovascular Health

Morris Notelovitz, M.D., Ph.D.

The recently observed increased incidence of cardiovascular disease in women probably relates to their increased longevity and the known effect that reproductive senescence has on the vascular intima and the lipid-lipoprotein profile of aging women. In 1983, the life expectancy for females at birth was 78.3 years and exceeded that for men by 7.3 years. For women who reach the age of 65, a further 18.8 years of longevity can be anticipated.³³ Although the role of ovarian function has been questioned,⁴⁸ many studies have shown a consistent relationship between high rates of coronary disease and an early menopause. In one study, women who had had a bilateral oophorectomy before age 35 were estimated to have a 7.2 times greater risk of being hospitalized for a myocardial infarction than matched normal premenopausal women.⁷³ This relationship is true for women who experience a natural menopause, too.

The incidence of cardiovascular disease in women followed on the Framingham study increased when women of the same age were compared according to their menopausal status.²⁵ Premenopausal women aged 50 to 54 years had 1.7 per 1000 episodes of coronary heart disease compared with respective rates of 6.8 and 4.4 episodes per 1000 in equally matched menopausal and postmenopausal women. Between age 65 and 69, the incidence of cardiovascular disease in women (22.1 per 1000) approximated that in men (26.7 per 1000).

The postmenopausal increase in cardiovascular disease is related to well-defined high risk factors for atherogenesis, such as increased plasma cholesterol level, decreased levels of high-density lipoproteins, and physical inactivity. Physically active men have fewer stigmata of coronary heart disease, and when they do, the stigmata are less severe and appear at an older age.⁶⁴ The same is true for

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women.⁷⁷ There are some who believe that physical inactivity per se is not a major risk factor,⁴⁷ but that it contributes to the underlying hemodynamic (hypertension) and metabolic (obesity, diabetes, hypercholesterolemia) changes associated with atherogenesis. The nutritive contribution to atherosclerosis is well established and has been consolidated by the significant decrease in cardiovascular disease brought about by increased physical activity, reductions in smoking, and, most important, reduced intake of cholesterol-rich foods.⁸⁴ During the period 1963 to 1981, there was an age-specific decrease in coronary mortality—due to lifestyle modification—that ranged from 44.8 per cent (at age 35 to 44) to 38 per cent (at age 55 to 64).⁸⁴

Estrogen therapy has the potential for inducing symptomatic cardiovascular disease by predisposing at-risk women to venous or arterial thrombosis. The use of oral contraceptives in older premenopausal women heralded their linkage to a greater likelihood of myocardial infarction, stroke, and hypertension—events attributed to the procoagulant activity of exogenous estrogen.⁵¹ Although the same relationship has not been found in postmenopausal women receiving hormone replacement, a practical clinical question arises: will the cardiovascular benefits of a judicious diet and an appropriate exercise program be compromised by hormone replacement therapy?

EXERCISE AND CARDIOVASCULAR DISEASE

The type, intensity, and duration of exercise needed to decrease the risk of coronary heart disease has been equated to 300 Kcal of activity per day above normal activity.³² Two parameters quantitate the response to this physical activity and can be used in everyday practice: the levels of plasma cholesterol and high-density lipoprotein (HDL) cholesterol and an estimation of aerobic power as measured by the total exercise time and the maximum oxygen uptake ($\text{VO}_{2\text{max}}$). The latter can be predicted by testing women on an exercising bicycle or measured directly by treadmill stress testing using a metabolic measuring cart.

LIPIDS, LIPOPROTEINS, AND EXERCISE

The plasma lipoproteins are the means whereby endogenous synthesized lipids are transported in the circulation. They are divided according to their gravitational density into four basic classes: chylomicrons, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). The latter is frequently subfractionated into HDL_2 and the more dense HDL_3 . The HDL_2 cholesterol component is higher in women and is inversely related to the development of coronary heart disease. Exercise stimulates HDL_2 levels and is higher in men and women runners than in sedentary controls.⁸⁸ The HDL-elevating effect of exercise is

thought to be caused by an increase in lipoprotein lipase, an enzyme responsible for the catabolism of triglyceride-rich lipoproteins. Lipoprotein lipase is found in greater concentrations in the skeletal muscle fibers (slow twitch) of endurance athletes. This may account for the slow increase in HDL levels in some persons, despite an appropriate exercise program.

Women who engage in regular endurance exercise do have higher HDL cholesterol levels than inactive women, and this is true for postmenopausal women, too.^{31,55,83} Postmenopausal long-distance runners and joggers had significantly greater levels of HDL cholesterol compared with a control group of relatively inactive females—79.8 mg per dl, 73.5 mg per dl, and 61.8 mg per dl, respectively. The lipid-lipoprotein profiles were minimally affected by exercise in a simultaneously studied group of exercising premenopausal women.³¹ The inability to make normal values more normal needs to be kept in mind when monitoring the HDL-cholesterol response of persons in prescribed exercise programs.

How much exercise is needed to improve the lipid-lipoprotein profile in typical sedentary postmenopausal women? In two recent studies, 12-week conditioning programs improved cardiovascular performance but not the lipid and lipoprotein profile.^{10,20} These discrepant results are explained by the duration of the exercise program and intensity of the exercise. For example, only when the weekly running mileage of 22 women increased from 3.5 miles to 44.9 miles (over a 7-month period) did the mean HDL-cholesterol levels increase from 53.5 to 58.5 mg/dl ($P < 0.01$).⁷⁵ To achieve a significant improvement in the HDL-lipoprotein moiety, at least 4 months of fairly strenuous activity (running 10 to 15 miles per week) is needed. With more moderate activity, such as walking, 30 miles per week for 3 months is needed before a significant increase in HDL-cholesterol levels will occur. With levels of activity at this intensity, compliance becomes a major issue, as it is so much easier to take an estrogen tablet than to run a mile.

AEROBIC POWER

Until fairly recently it was thought that exercise would not benefit middle-aged people and that the decline in cardiorespiratory function is such that the benefit from exercise would be compromised when compared with equivalent degrees of activity in younger subjects.⁴⁴ Furthermore, it was postulated that menopause per se could be responsible for the decrease in aerobic power in women over the age of 50.

As with men, women have an age-related decrease in cardiorespiratory fitness. One hundred and sixty-three healthy sedentary females between the ages of 35 and 75 years had a $\text{VO}_{2\text{max}}$ testing after being screened for cardiovascular normalcy by a 12-lead EKG stress test and physical examination. The $\text{VO}_{2\text{max}}$ was elicited using a modi-

fied Balke treadmill procedure.⁵⁸ Each subject's $\dot{V}O_{2\max}$ was directly measured using a Beckman Metabolic Measurement Cart. A decrement of 5.5 per cent of $\dot{V}O_{2\max}$ occurred with each succeeding decade between ages 35 and 75. This observation approximates with the generalization that sedentary individuals have a 1 per cent loss of $\dot{V}O_{2\max}$ per year with age, especially after age 50. This loss of aerobic power is not related to the menopause per se. In a recent study, women aged 45 to 55 had their $\dot{V}O_{2\max}$ predicted by means of a submaximal bicycle ergometer test.⁵⁸ They were divided according to whether they were still menstruating. Their pre- and postmenopausal status was confirmed by hormonal analysis and by their menstrual pattern. No significant difference was found in the estimated $\dot{V}O_{2\max}$ — 27.4 ± 6.3 ml per kg per min for the menstruating group versus 26.3 ± 4.7 ml per kg per min for the nonmenstruating group ($P > 0.05$).⁵⁸ As a generalization, women usually achieve maximal $\dot{V}O_2$ values in the decade 20 to 29 years; by age 50 to 65 years the values are decreased by almost 30 per cent.¹⁷ The rate of decline is slower in physically active men and women. Normative values for varying degrees of aerobic fitness in women are listed in Table 1.

Menopausal women can achieve physical fitness. Premenopausal women (mean age: 41 years) trained 9 weeks and improved their $\dot{V}O_{2\max}$ by 12.1 per cent; similarly trained postmenopausal women (mean age: 57 years) improved their $\dot{V}O_{2\max}$ by 19 per cent.¹⁶ This result has been confirmed by others,⁶⁶ including two studies conducted at The Center for Climacteric Studies. Moderate exercise (walk-jogging three times a week for 12 weeks) resulted in a significant increase in the maximal oxygen consumption, time on the treadmill, and the time to get to 90 per cent of maximal oxygen consumption, when compared with age-matched female controls.²¹ More recently, 63 postmenopausal women were evaluated over a 1-year period during a structured program that involved three weekly 20-minute treadmill, ergometer, or Nautilus (muscle strengthening) sessions. Two nonexercising groups were included: an age-matched

Table 1. *Guidelines for Fitness Assessment by $\dot{V}O_{2\max}$ (ml/kg/min) of Healthy Women Aged 30 to 70 Years*

	POOR	FAIR	AVERAGE	GOOD	EXCELLENT
30-39	<20	20-27	28-33	33-44	45+
40-49	<17	17-23	24-30	31-41	42+
50-59	<15	15-20	21-27	28-37	38+
60-69	<13	13-17	18-23	24-34	35+

Adapted from Exercise Testing and Training in Apparently Healthy Individuals: A Handbook for Physicians. The Committee on Exercise. The American Heart Association, 1972.

nontreatment group and a slightly younger group on hormone replacement therapy. Aerobically trained subjects were exercised between 70 and 85 per cent of their maximal heart rate. Significant improvements in both $\text{VO}_{2\text{max}}$ and time on the treadmill were recorded and maintained by the bicyclers and the treadmill groups (Tables 2 and 3).⁵⁹

The anticipated degree of improvement in aerobic power is inversely related to the subject's initial level of fitness and the intensity/frequency of the training program. The lower the degree of fitness, the greater the subsequent improvement. For example, the postmenopausal women in Cowan and Gregory's study¹⁶ had a 19 per cent improvement in $\text{VO}_{2\text{max}}$; the mean baseline $\text{VO}_{2\text{max}}$ of their subjects was only 12.6 ml per kg per min compared with a baseline VO_2 value in the Gainesville study that ranged from 26 to 27 ml per kg per min—values far in excess of the previous study's 15.0 ml per kg per min end-point level. The percentage gain in aerobic power from a number of different studies is summarized in Table 4. Values range from 8 to 30 per cent. With only one exception, the duration of the training program was less than 14 weeks. The best improvement was obtained in programs whose duration of exercise exceeded 30 minutes. These results do not reflect the true potential of middle-aged women engaged in long-term intensive exercise programs, nor do they consider a most important practical real-life issue of exercise: compliance.

Exercise is good. According to a recent cross-sectional study,⁷¹ active women had a cardioprotective effect of one decade when compared with sedentary women. The average duration in mean $\text{VO}_{2\text{max}}$ of active 40- to 49-year-old women was higher than sedentary 30- to 39-year-old women; active 50- to 59-year-old women had values similar to 40- to 49-year-old women. One way of encouraging women to exercise is to use cardiorespiratory fitness assessments as a means of demonstrating improvement in aerobic function before the physical benefits of exercise are appreciated. Bruce and associates⁸ recently reported that 63 per cent of their patients attributed a change in one or more risk factors in health habits to a graded exercise test. Persons with an abnormal result were motivated the most. Maximal oxygen uptake tests need to be performed in a specially equipped laboratory and are not suited to everyday clinical practice. Submaximal testing, on the other hand, is more ideally suited to the practicing physician and his patients. Several studies have shown that predicted VO_2 testing correlates well with observed maximal testing when corrected for age,^{12,22} but none of these studies involved climacteric women. To test this relationship in postmenopausal females, 29 women participating in an ongoing exercise program had both a treadmill and an ergometer test.⁵⁸ The measured and predicted $\text{VO}_{2\text{max}}$ results were found to correlate closely ($r = 0.789$).

Submaximal testing can thus be used both as a screen to determine the cardiorespiratory fitness of climacteric women and to monitor the response to prescribed exercise. Patients at high risk for car-

Table 2. *Response of Climacteric Women (Mean Age 56 Years) to Intensive Structured Exercise*

	AGE	NO.	BASELINE	3 Mos.	6 Mos.	12 Mos.	% DIFFERENCE BASELINE VS. 12 Mos.
Nautilus	59.3 ± 6.7	13	26.0 ± 5.2	26.1 ± 4.7	26.5 ± 4.0	26.2 ± 3.9	.8
Treadmill	54.9 ± 6.9	10	27.1 ± 2.7	29.5 ± 2.8	30.5 ± 2.8	29.5 ± 2.4	8.9
Ergometer	55.9 ± 6.9	10	26.7 ± 4.7	28.9 ± 4.1	30.2 ± 4.1	30.0 ± 4.8	12.4
Control	62.0 ± 7.1	14	26.5 ± 4.7	26.1 ± 6.0	25.9 ± 5.9	26.2 ± 5.8	-1.1
Hormone	48.4 ± 7.2	16	26.6 ± 3.9	26.3 ± 3.7	26.4 ± 4.2	25.1 ± 3.9	-5.6

Mean (±SD) Maximal oxygen uptake (ml/kg/min).

From Notelovitz M, Fields C, Caramelli K, et al: Alternatives to hormone therapy. Presented at the Eleventh World Congress of Obstetrics and Gynecology, Berlin, October 1985.

diovascular disease and those classified as having fair to poor fitness (as measured by ergometry) require more detailed evaluation before embarking on a prescribed exercise program. A nomogram is also very useful; when used together with age-adjusted tables listing cardiorespiratory fitness for women, potential exercise candidates obtain a good index of both their current fitness status and the goals they need to reach (see Table 1).

STRENGTH TRAINING

Several cross-sectional studies have shown a loss of muscle strength with age, beginning after the third decade of life and amounting to a decline of 16.5 per cent or greater.¹⁹ The loss is greater in women.⁵⁴ This loss of muscle tissue is related to a number of important metabolic activities. Tzanoff and Norris⁸² maintain that muscle mass may be wholly responsible for the age-related decrease in basal metabolic rate. The average $\text{VO}_{2\text{max}}$ of older men was 22 per cent lower when compared with younger men; this difference decreased to only 8 per cent when the values were expressed in terms of ml per kg per min of muscle as determined by 24-hour urine creat-

Table 3. *Response of Climacteric Women (Mean Age 56 Years) to Intensive Structured Exercise*

	AGE	NO.	BASELINE	3 Mos.	6 Mos.	12 Mos.	% DIFFERENCE BASELINE VS. 12 Mos.
Nautilus	59.3 ± 6.7	13	12.1 ± 3.2	12.2 ± 2.5	12.9 ± 2.4	12.5 ± 2.4	5.3
Treadmill	54.9 ± 6.9	10	12.5 ± 1.6	14.2 ± 2.1	15.2 ± 2.0	15.3 ± 2.1	21.5
Ergometer	55.9 ± 7.9	10	13.0 ± 3.1	14.1 ± 3.0	14.5 ± 3.0	15.2 ± 3.3	17.4
Control	62.0 ± 7.1	14	12.2 ± 3.3	11.6 ± 3.6	12.2 ± 4.0	12.1 ± 3.4	-.95
Hormones	48.4 ± 7.2	16	13.4 ± 2.4	12.6 ± 2.3	13.0 ± 2.3	12.3 ± 2.2	-7.7

Mean (±SD) Total exercise time (MIN:SEC).

From Notelovitz M, Fields C, Caramelli K, et al: Alternatives to hormone therapy. Presented at the Eleventh World Congress of Obstetrics and Gynecology, Berlin, October 1985.

Table 4. Improvement in O_2 Uptake Following Aerobic Training Programs in Women over the Age of 50 Years

	NO. OF PATIENTS	DURATION OF EXERCISE PER SESSION (Min)	FREQUENCY OF EXERCISE PER WEEK	INTENSITY OF EXERCISE	DURATION OF TRAINING PROGRAM (WEEKS)	% GAIN IN O_2 UPTAKE
Kilbom	13	30	2-3	70%*	7	8
Adams and Devries	17	50	3	85%†	12	20.8
Sidney et al.	25	60	4	HR 120-150/min	7	>30
Sidney and Shephard	28	55	3	60-80%	14	17
Cowan and Gregory	14	50	4	80%†	9	18.9
Notelovitz et al.	10(T)	20	3	70-85%†	52	8.9
	10(E)	20	3	70-85%†	52	12.4

* $\dot{V}O_{2max}$

†Max Heart Rate

T: Treadmill

E: Ergometer

Adapted from Cowan MC, Gregory LW: Responses of pre- and postmenopausal females to aerobic conditioning. Med Sci Sports Exerc 17:138, 1985.

inine measurements. Increasing muscle mass can thus play an important role in determining body composition: a 5 per cent increase in the basal metabolic rate of a 160-pound man results in an additional expenditure of 75 to 80 Kcal/day, the equivalent of about 8 pounds of body fat. Muscle is also an important determinant of carbohydrate utilization. The rate of glucose removal is more rapid in physically active persons, and the amount of insulin needed significantly reduced.⁴³ This is reputed to be caused by enhanced sensitivity of insulin receptors in skeletal (and adipose) tissue. Obesity and diabetes are two atherogenic-related diseases commonly encountered in postmenopausal women.

Weight training in women has shown that improvement in strength can be obtained with a loss of adipose tissue and with relatively little muscle hypertrophy. These studies have involved young women and/or trained athletes.^{6,85} It is not known whether muscle strengthening exercises will enhance the metabolic function of postmenopausal skeletal muscle, and if so, to what degree. Strength training does not improve cardiorespiratory function (see before), a finding confirmed by studies done in middle-aged men.³⁹ Much additional research is obviously needed in this area. Clinical experience indicates that muscle-strengthening exercises—apart from any possible effect on metabolism—have an important role in building up the muscle of sedentary persons prior to their starting an aerobic program. The improved muscle tone lessens the likelihood of trauma and gives subjects more confidence to exercise. Some form of muscle-strengthening program should be incorporated in all postmenopausal exercise prescriptions and precede the introduction of the aerobic component by 8 to 12 weeks.

DIET AND CARDIOVASCULAR DISEASE

Food has an atherogenic potential clearly linked to the cholesterol and saturated fat content of the diet.¹⁵ The diet is especially important in postmenopausal women, since the LDL-cholesterol values in postmenopausal women rise progressively after the menopause and are not accompanied by a compensatory increase in HDL-cholesterol levels. LDL-cholesterol levels in postmenopausal women after age 50 actually exceed those in men, although the LDL/HDL-cholesterol ratio still remains more favorable in women at all ages.³⁶

There is a growing consensus that a cholesterol and LDL-cholesterol lowering diet will reduce the high prevalence of coronary heart disease. This has been associated with the LDL receptor hypothesis: diets high in cholesterol and saturated fats suppress the hepatic synthesis of LDL receptors, whereas diets low in fats are associated with increased numbers of LDL receptors and the ability to degrade this atherogenic LDL moiety.⁷ There is an inverse relationship between LDL and HDL-cholesterol levels, with the latter being cardioprotective. Care needs to be exercised when assessing the rela-

tive atherogenic risks of these factors, as it is the ratio between HDL-cholesterol/total cholesterol or HDL/LDL-cholesterol rather than the absolute values of any single fraction that probably constitutes the real risk for cardiovascular disease.²³

There appears to be a threshold for serum cholesterol levels, below which cardiovascular disease rarely develops. This has been estimated to lie somewhere between 125 and 165 mg per dl as found in populations where coronary heart disease is unknown (Tarahumara Indians) or very low (Japanese). The mean serum cholesterol value in the United States, for example, is 205 mg per 100 ml. Serum cholesterol values are associated with varying annual mortality rates from coronary heart disease. In Japanese women, the mortality is 50 per 100,000 versus 264 per 100,000 in the United States. In Northern Ireland, the incidence is 360 per 100,000.⁷⁹ A recent study⁵³ has shown that the relative risk for coronary heart disease mortality rises once the cholesterol level exceeds the 20th percentile, but becomes especially pronounced above the 85th percentile. Half of the observed deaths from coronary heart disease were found in individuals with cholesterol levels above 180 mg per dl, and half of these deaths, in turn, with values in excess of 253 mg per dl. These findings support the recent recommendation of the NIH Consensus Development Conference on the need to lower blood cholesterol to prevent heart disease.¹⁴

How can this be achieved? As with exercise, the diet must be palatable so that it will be readily adopted if it is to become a permanent lifestyle change. The American Heart Association (AHA) and other advisory groups proposed a reduction in the total fat intake from the current 40 per cent of total calories in the diet to 30 per cent of calories, and that the saturated fatty acid content be decreased to below 10 per cent of calories. The dietary cholesterol needs to be lowered to less than 300 mg per day. This is the so-called American Heart Association Phase I Diet. Additional recommendations include increasing the intake of carbohydrates and polyunsaturated fatty acids. The latter have an intrinsic ability to decrease total cholesterol levels over and above that obtained simply by removing saturated fatty acids from the diet.²⁶ By further decreasing the total fat intake to 20 per cent of the total caloric intake, an optimal cholesterol lowering diet was postulated (AHA Phase III Diet). However, a recent study confirmed that whereas polyunsaturated fatty acids, monounsaturated fatty acids, and carbohydrate will lower plasma cholesterol and LDL-cholesterol levels, the mix of these nutrients is important, as a low-fat high-carbohydrate diet can raise triglyceride levels while increasing the carbohydrate and polyunsaturated fatty acid component of the diet and may actually decrease the HDL-cholesterol level.²⁶ Increasing polyunsaturated fatty acids in the diet has also been associated with the development of gallstones⁸⁰ and possibly breast and colonic cancer.¹³ Because of this, and the greater discipline and self-control needed to meet the dietary goals of a 20 per cent fat diet, the AHA Phase I Diet is probably best suited to most

women who are not obese and do not have markedly elevated cholesterol levels.

Since the atherogenic potential of food depends on the cholesterol and saturated fat content, a cholesterol/saturation fat index (CSI) has been developed¹⁵ and serves as a very useful guide to compare different foods and recipes. Appreciation of this concept is most important since some foods, like shellfish, are high in cholesterol, but low in saturated fats, whereas certain vegetables (hydrogenated vegetable shortening or palm and coconut oils) are free of cholesterol but very high in saturated fats. Cheeses and red meats are high in both cholesterol and saturated fats. A low CSI is indicative of low saturated fat and cholesterol content, and hence, low atherogenicity. The CSI for 100 gm of some foods are fish-4, shellfish-6, poultry-6, beef-13, egg white-0, and egg yolk (two whole eggs)-29. By comparison, cereals, potatoes, pasta, rice, and many vegetables have values of 0. Bread and legumes have a CSI of less than 1.

Epidemiologic studies have shown that the diet of Eskimos—which is rich in fish oils—is associated with a lower incidence of coronary heart disease. The addition of relatively small amounts of fish has had a noticeable effect in reducing the coronary heart disease risk in Europeans⁴⁶ and North American populations, too.⁷⁸ The beneficial effect has been attributed primarily to the omega-3 fatty acid eicosapentaenoate and its ability to lower cholesterol and triglyceride blood levels⁶⁷ and to modify the biosynthesis of the vasoactive prostaglandins, thromboxane and prostacyclin.⁴⁵ Eicosapentaenoic acid competes with arachidonic acid as a substrate for the enzyme cyclooxygenase. The predominant end product of arachidonate in platelets is the potent vasoconstrictive thromboxane A_2 ; the corresponding product of eicosapentaenoate is thromboxane A_3 , which is virtually biologically inert. Both prostacyclin I_2 (derived from arachidonate) and prostacyclin I_3 (derived from eicosapentaenoate) are active vasodilators and platelet inhibitors. The theoretical net effect is a cardioprotective tendency towards vasodilation and diminished platelet adhesiveness. Although the addition of eicosapentaenoate-containing fish oil to the diet will alter the synthesis of thromboxane and prostacyclins, the dose needed is large (10 gm per day) and does not equate to the simplicity and greater efficacy of taking a single 325 mg tablet of aspirin. Much more information is needed before the role of the omega-3 fatty acids can be quantitated; in the interim women should be encouraged to include fish in their diets, especially as a substitute for cholesterol-rich red meats. As little as three portions of fish per week may be all that is required.

The importance of calcium for normal osteogenesis and bone mineral maintenance is clearly defined. More recently, some studies^{30,50} have shown an inverse relationship between dietary calcium and blood pressure. Some workers⁴ have shown that supplementation with 1 gm of elemental calcium daily lowers the diastolic pressure by 5 per cent in young women and 9 per cent in young men. Others⁴⁹ have shown that this effect is primarily found in hyperten-

sives. It is still unclear whether an adequate dietary (or supplementary) calcium intake will prevent hypertension,⁴⁰ but it does seem prudent to use this potential benefit as an additional encouragement for women to have a calcium-replete diet.

In summary, physical activity and dietary modification can go a long way toward protecting women against atherogenic disease. Intervention at an early age will obviously produce the best results, but it is never too late to start. Physicians need to familiarize themselves with advances being made in exercise physiology and nutrition and to use this information to give patients an appropriate lifestyle prescription.

ESTROGENS, COAGULATION, AND CARDIOVASCULAR DISEASE

Long-term estrogen replacement reduces bone mineral loss, and its clinical use is justified where indicated. Based on the experience of oral contraceptive usage in older premenopausal women and the alleged procoagulant potential of estrogen (its ability to reduce plasma levels of antithrombin III), the possibility of a benefit in one metabolic compartment being compromised by an unacceptable risk in another needs to be considered. Fortunately, clinical experience has shown that postmenopausal estrogen replacement therapy is safe. Except for two reports,^{22,42} numerous epidemiologic studies have failed to find an association between estrogen usage in postmenopausal women and a greater cardiovascular risk.^{65,66,74} One study²⁹ suggested that the incidence of cardiovascular disease may actually be lowered by early and consistent hormone replacement, a viewpoint that has been confirmed more recently by Henderson and colleagues.³⁷ In one of the negative studies, 36 of the 57 patients had some evidence of cardiovascular disease before starting hormonal therapy.⁴² This hardly implicates estrogen as an initiator of cardiovascular disease, but it does confirm the need for care in prescribing estrogen to patients with documented atherogenic disease.

COAGULATION, ANTICOAGULATION, AND THROMBOEMBOLIC DISEASE

To fully appreciate the true cause-and-effect potential between estrogen usage and thromboembolic disease, and to place in clinical perspective changes observed in the coagulation profile of estrogen-treated women, there are three points that need to be appreciated: (1) there are no tests—single or in combination—that measure hypercoagulability or have the ability to predict blood clot formation; (2) there are no studies that have shown a cause-and-effect relationship between a procoagulant alteration in the coagulation profile and the development of a thrombus; and (3) the increase of a procoagulant component, such as factor X, may be balanced by an increase in

plasmin or the fibrinolytic activity of the vascular intima.⁵² In short, a blood clot will only form when changes in blood flow and an enhancement of the coagulation cascade are superimposed on an area of intimal damage in the absence of normal anticoagulant and fibrinolytic activity. The integrated relationship between platelet activity, coagulation, and fibrinolysis is summarized in Figure 1.

INTIMAL DAMAGE

A thrombus is unlikely to develop as long as the intima is intact. When it is damaged, certain components (collagen, for example) are exposed that stimulate thrombogenesis. Earlier data that suggested endogenous and exogenous estrogen as common denominators in the formation of intimal lesions have been discounted by the observation of intimal proliferation in other clinical conditions unassociated with excess estrogen.⁴¹

Women with defective fibrinolytic activity in the vessel wall may be more susceptible to vascular accidents. Studies in women experiencing recurrent thrombosis while using oral contraceptives² and postmenopausal women treated with ethinyl estradiol³ were found to have normal blood coagulation profiles and a defect in the endothelial fibrinolytic system. A defective vascular fibrinolytic system has been

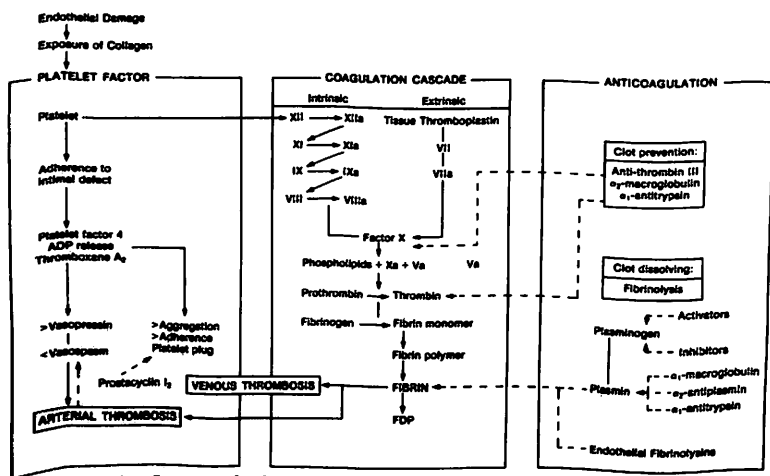


Figure 1. Integrated relationship between platelet activity, coagulation, and fibrinolysis. Broken lines = inhibitory; solid lines = stimulatory. (Modified from Notelovitz M, Ware M: Coagulation risks with menopausal estrogen therapy. In Studd J (ed): Progress in Obstetrics and Gynecology. Vol 2. Edinburgh, Churchill-Livingstone, p. 228, 1982; with permission.)

found in as many as 30 to 50 per cent of persons with proven idiopathic venous thrombosis.⁵ Thus, some individuals are predisposed to blood clot formation because of an inherited vascular defect. Unfortunately, there are no readily available means of detecting this abnormality, but there is one potential preventive: exercise. Exercise increases the fibrinolytic response in healthy adults and is an important factor to consider when prescribing estrogens.⁸⁷

Blood flow has also been associated with decreased fibrinolytic activity and an impaired defense against fibrin deposition. This is consistent with the clinical association between venous stasis and deep venous thrombosis. An estrogen-induced increase in pelvic (vaginal) blood flow has been established,¹ but the effect on peripheral blood flow still needs to be defined.

The most important mediator of vascular tone is the homeostasis between prostacyclin and thromboxane (see previous discussion). Animal experiments have shown that progesterone seems to have a protective effect, in that prostacyclin production is either unchanged or increased.⁷² Estrogen on its own has a tendency to decrease endothelial prostacyclin synthesis (Table 5).¹⁸ Silfverstolpe and co-workers^{78a} examined the effects of synthetic (ethinyl estradiol) and natural (estradiol valerate) estrogens and levonorgestrel on prostacyclin and thromboxane activity in postmenopausal women. They showed that only the synthetic estrogens (ethinyl estradiol) increased prostacyclin activity. This very important issue still needs to be clarified; it is the balance between the stimulation or inhibition of the vasodilating and antiplatelet aggregating prostacyclin, and its antagonist, thromboxane A₂, which will determine the overall effect. The interaction between these two metabolic products is also influenced by other drugs. The intermittent use of a low-dose aspirin regimen (30 mg every second or third day) has been shown to alter the balance in favor of greater prostacyclin activity and should be considered in women at relative risk, for example, in women with varicose veins.

Table 5. *Hormone Replacement Therapy and Blood Clot Formation*

ESTROGEN	PARAMETER	PROGESTOGEN
>	Blood flow	—
No change	Intima	No change
>; No change	Coagulation cascade: II; VII; IX; X	No change
<; No change	Anti-coagulation anti-thrombin III	—
No change	Clot-dissolving plasminogen	>
? >	α_2 anti-plasmin	<
? >	Prostaglandins; thromboxalic A ₂ :	—
<	prostacyclin	>; no change

PLATELET ACTIVITY

Platelet activity is a primary determinant of coagulation via its effect on thromboxane A_2 synthesis and platelet aggregation and adhesiveness and by its activation of factor XII, the initiator of the coagulation cascade. The known effect of sex steroids on platelet function is incomplete and contradictory, owing in part to the technical difficulty of the various tests of platelet function and their relatively poor reproducibility.

A fairly consistent feature has been a decrease in the platelet count.⁵⁷ The clinical significance of this change is not apparent, since the values are invariably within the range of normal for a given laboratory. Platelet aggregation and adhesion are not usually affected by estrogen replacement, although one group has reported increased platelet aggregation in women treated with conjugated estrogens.⁶⁹ This increase persisted when assessed 18 months after starting hormonal treatment. A similar effect was noted after treatment with estriol succinate, an estrogen known to have minimal adverse systemic effects.⁸¹

The correlation between in-vitro platelet function and in-vivo platelet behavior must be interpreted cautiously, because the tests are highly artificial, and the results may bear little relation to the vascular event. As an example, platelet adhesiveness has not been useful in detecting thrombosis after surgery.

COAGULATION CASCADE

The coagulation cascade is divided into an intrinsic and an extrinsic system, the end result being the formation of the prothrombin-converting principle and the rapid conversion of prothrombin to thrombin (see Fig. 1). The latter interacts with fibrinogen, producing a soluble fibrin monomer, which in turn is polymerized into a fibrin polymer, the final insoluble blood clot. A number of tests are used to evaluate different aspects of this process, none of which is truly predictive of a potential or actual pathologic event. Despite this, a large and contradictory literature has been based on the interpretation of these tests. It behooves the clinician to become familiar with the various tests, what they measure, and what the clinical interpretation should be. Partial thromboplastin time (PTT) and the prothrombin time (PT) are measurements of the intrinsic and extrinsic pathways, respectively, and constitute the so-called dynamic tests of coagulation. Individual factors can also be measured, but these tests are more complex and are not usually available as a clinical service. The normal range for the partial thromboplastin time varies with the laboratory and techniques, but is usually between 45 and 60 seconds. The normal value for the prothrombin time at 37°C is 12 seconds. Shortening of these times indicates accelerated coagulation, but should not be interpreted in

the same way, as an increase in these times is used clinically for determination of anticoagulation. Another method of assessing abnormal coagulation is to test for intravascular coagulation. This is characterized by decreased platelet counts, increased amounts and/or activity of fibrinogen, and increased concentration of fibrin degradation products. Recently, radioimmunoassays have been developed for subfractions of the fibrin degradation products—fibrinopeptides A, D, and E. A very strong correlation has been noted between fragment E in patients with a proven pulmonary embolism and fibrinopeptide A in patients with venous thrombosis. Because many of the other tests and clinical signs of thromboembolic disease are unreliable, these radioimmunoassays of fibrinogen degradation products may prove to be important screening tests of ongoing intravascular coagulation.

As summarized recently,⁶³ the majority of reports indicate no acceleration of the intrinsic clotting system with the use of either the partial thromboplastin time or other less common methods, such as the whole-blood clotting. A decrease in prothrombin time has been noted in some studies, but long-term treatment with the same natural estrogen (estriol succinate) revealed no apparent change.⁸¹

Virtually all of the individual clotting factors that can be tested have been found to be elevated in women using exogenous estrogen: levels of fibrinogen, the vitamin K-dependent factors—prothrombin and factors VII, IX, and X—and factor XII have been found to be elevated most frequently. This effect is probably related to the potency rather than the type of estrogen; it is more marked with ethinyl estradiol and least with estriol-containing preparations.⁶³ The route of administration is also important, as illustrated by the absent elevation in fibrinogen complexes of high molecular weight and other clotting factors in women treated with estrogen skin patches.¹¹ In the latter study, it was pertinent to note that the same was true for equivalent doses of conjugated estrogen.

Elevated levels of clotting factors do not indicate a functional hypercoagulable state for the following reasons: the clotting factors circulate as proenzymes or as cofactors to other enzymes and are themselves inactive until a suitable clot-promoting surface has been provided. All of the clotting factors circulate in plasma far in excess of that actually required for clot formation. For example, although the level of factor VIII is present in a wide range—60 to 200 per cent in a healthy population—only 25 per cent of this activity is actually needed for hemostasis. Conversely, individuals will only bleed after their measured clotting factors have fallen to below 30 to 40 per cent of normal levels.⁵² Finally, the tests that measure the various factors do not differentiate between the proenzyme and the activated forms, nor is there any evidence that the infusion of clotting factors in their proenzyme state will precipitate a thrombogenic event. A parallel can be drawn from estrogen and hepatic renin-substrate and the relatively infrequent occurrence of a directly related elevation in blood pressure.

The effect on the various clotting factors referred to above appears to be estrogen-mediated, because the use of progesterone alone—for as long as 2 years—has not been associated with a rise in clotting factors.⁷⁰

ANTICOAGULATION

The fluidity of blood is maintained by potent natural anticoagulants, of which antithrombin III appears to be the most important. Antithrombin III accounts for at least 50 per cent of the anticoagulant activity. It is catalyzed by heparin and in its complexed form neutralizes thrombin instantly. Antithrombin III, together with some of the other less potent thrombin inhibitors such as α_1 -antitrypsin and α_2 -macroglobulin, can be measured immunologically or by their biological activity. These coagulation inhibitors can be regarded as clot "prevents."

Deficiency of antithrombin III is associated with an increased liability of thrombosis. The level at which antithrombin III deficiency would cause thrombus formation is not known, but it would probably have to be reduced to about 50 per cent of its normal activity. When interpreting the clinical significance of depressed antithrombin III levels, two points need to be considered: the level of its activity and whether it was measured in plasma or serum. Antithrombin III assayed in serum is a measurement of the amount of antithrombin left after clotting, and not that consumed during clotting. This accounts for many of the reports that showed significant lowering of antithrombin III activity with exogenous estrogens and, as with the coagulation factors, has no real bearing on the actual risk of inappropriate thrombus formation.⁶³ As with liver enzymes, antithrombin III levels are relatively unaffected by parenterally administered estrogens.¹¹

FIBRINOLYSIS

Fibrinolysis involves the enzymatic degradation of fibrin and fibrinogen. The endothelium has fibrinolytic activators that are continuously liberated into the bloodstream and counteract thrombosis by removing fibrin deposits. In addition, there is a plasma fibrinolytic system that has five distinct components: plasminogen, plasmin, plasminogen activators, plasminogen activator inhibitors, and plasmin inhibitors.

Clot lysis is activated by the conversion of plasminogen to plasmin, the active fibrinolytic principle. Plasmin digests both fibrinogen and fibrin but has a relative substrate specificity for the latter. Plasminogen is a β -globulin synthesized in the liver and, as such, is highly responsive to sex steroids.⁶³ In a recent study, for example, conjugated estrogens significantly increased plasminogen antigen and

plasminogen activity in surgically menopausal women,⁶¹ an effect that may be enhanced by combined estrogen/progestogen therapy.⁶² As with the interpretation of changes in the coagulation profile, the clinical significance of alterations in fibrinolytic activity needs to be kept in perspective.

AGING, MENOPAUSAL STATUS, AND COAGULATION

Elderly women are thought to be at higher risk of thromboembolic disease than younger women. Investigators have shown that platelet adhesion and aggregation increase with age,⁹ as well as levels of fibrinogen and factors V, VII, XI and XII.²⁷ Fibrinolytic activity has been shown to decrease with age but has also been reported to be unchanged or increased.²⁸ These changes are affected by the menopausal status per se. A recent study observed increases in antithrombin III antigen, α_1 -antitrypsin activity, and plasminogen activity⁶⁰ in both surgically and naturally menopausal women. These changes together with the moderate influence of exogenous estrogens on hemostasis may help explain why estrogen replacement does not appear to cause thrombosis in older women.

LIFESTYLE, SEX STEROIDS, AND COAGULATION

The relationship between exercise and exogenous estrogens on coagulation in menopausal women has not been studied. Exercise does, however, have an anticoagulant effect and has even been shown to act with certain oral contraceptives to increase fibrinolytic activity—as measured by plasminogen activators—over and above that induced by the oral contraceptive itself.^{34,35} A similar positive effect of exercise has been reported in other studies involving women using oral contraceptives as measured by decreased levels of α_2 -plasmin inhibitor.³⁸ It is thus highly improbable—but as yet unproved—that estrogen replacement will negate the positive hemodynamic and metabolic effects of exercise on the cardiovascular system. Smoking, however, does pose a potential thrombogenic risk. For example, smoking and oral contraceptive use appear to act synergistically to increase the risk of myocardial infarction. This is especially true for women who are at higher risk because of their age. Thus, in one study,⁷⁶ for women aged 35 to 44, the excess annual death rate was 1:6700 in nonsmokers and 1:2000 in smokers; at 45 years and above, the risks were 1:2500 and 1:500. One of the possible mechanisms is the recent finding linking the inhalation of nicotine-containing tobacco smoke with a reduction in vascular prostacyclin production.⁵⁶

Estrogen replacement has been used very safely by millions of women. Yet, there will be a small minority of women in whom a venous or arterial thrombus will develop. Given the other benefits of

estrogen replacement therapy, this risk is extremely small and can be reduced to a minuscule level by encouraging postmenopausal women to eat judiciously and well and to engage in a regular and meaningful exercise program. Estrogen replacement therapy will not compromise a healthy lifestyle.

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