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Natural Progesterone, but Not Medroxyprogesterone Acetate, Enhances the Beneficial Effect of Estrogen on Exercise-Induced Myocardial Ischemia in Postmenopausal Women

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OBJECTIVES We sought to compare the effects of estrogen/transvaginal progesterone gel with estrogen/medroxyprogesterone acetate (MPA) on exercise-induced myocardial ischemia in postmenopausal women with coronary artery disease or previous myocardial infarction, or both.

BACKGROUND Estrogen therapy beneficially affects exercise-induced myocardial ischemia in postmenopausal women; however, women with an intact uterus also take progestin to protect against uterine malignancies. The effects of combination estrogen/progestin therapy on myocardial ischemia are unknown.

METHODS Eighteen postmenopausal women (mean ± SD age 59 ± 7 years) were given 17-beta-estradiol in single-blinded manner for four weeks (1 mg/day for three weeks then 2 mg/day for one week). Estradiol (2 mg/day) was then continued, and the patients were randomized (double-blind) for 12 days to either transvaginal progesterone gel (90 mg on alternate days) and oral MPA placebo (10 mg/day), or vice versa. After another two weeks on estradiol alone, the patients crossed over to progestin treatment and repeated the protocol on the opposite treatment. Patients underwent treadmill exercise testing after each estradiol phase and at day 10 of each progestin phase.

RESULTS Exercise time to myocardial ischemia increased after the first estrogen phase as compared with baseline (mean difference with 95% confidence interval [CI]: 72 s [34 to 110], $p = 0.001$), and was increased by combination estradiol/progesterone therapy as compared with estradiol/MPA therapy (92 s [35 to 149], $p = 0.001$)). Two patients (11%) were withdrawn while taking estradiol/MPA owing to unstable angina.

CONCLUSIONS Combination estrogen/transvaginal progesterone gel increases exercise time to myocardial ischemia, as compared with estrogen/MPA. These results imply that the choice of progestin in women at higher cardiovascular risk requires careful consideration. (J Am Coll Cardiol 2000;36:2154–9) © 2000 by the American College of Cardiology

Cardiovascular disease is the major cause of death in postmenopausal women, with a fatality rate that is double that of all forms of cancer. There is a wealth of epidemiologic evidence indicating that postmenopausal estrogen therapy can significantly reduce the risk of death due to cardiovascular disease in postmenopausal women (1). However, women with an intact uterus must also be given progestin to prevent the increased risk of endometrial hyperplasia and cancer seen with estrogen-only therapy. One large epidemiologic study suggests that estrogen combined with progestin results in a significantly decreased risk of death from cardiovascular disease (2); however, this study was not able to distinguish between different progestins. The Heart and Estrogen Replacement Study (HERS) has reported a null effect of long-term combined treatment with conjugated equine estrogen and medroxyprogesterone acetate (MPA) in postmenopausal women at increased risk of coronary artery disease (CAD) events, as well as a potential increase in the risk of myocardial infarction during the first year of therapy (3). One of a number of reasons for the null effect may involve inhibition of the beneficial effect of estrogen by MPA. Investigation of the effect of progestins in women with established CAD is therefore important.

Treatment with short- and long-term estrogen improves exercise time to myocardial ischemia in postmenopausal women with proven CAD (4,5). An anti-ischemic effect of estrogen has been demonstrated using different experimental techniques in postmenopausal women (6,7). A variety of estrogens have anti-atherogenic properties in various models (8,9). Studies have consistently demonstrated that MPA antagonizes the inhibitory effects of conjugated equine estrogens on coronary artery atherosclerosis in cynomolgus monkeys (10,11). Estrogen can protect against coronary vasoconstriction to acetylcholine (12,13); however, recently it has been shown that MPA can interfere with this protection against coronary vasospasm (14). There is evidence that progesterone can result in endothelium-independent relaxation of coronary arteries at high concentrations (15), and that natural progesterone, unlike MPA, does not antagonize the effect of estrogen on coronary atheroma (10) or coronary vasospasm (14). The choice of

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Abbreviations and Acronyms

CAD = coronary artery disease
CI = confidence interval
ECG = electrocardiographic
FSH = follicular stimulating hormone
HERS = Heart and Estrogen Replacement Study
MPA = medroxyprogesterone acetate

progestin, particularly in patients with established CAD, may be very important. We therefore undertook a study to compare the effects of adding oral MPA or transvaginal progesterone gel to estrogen therapy on exercise-induced myocardial ischemia in postmenopausal women with proven CAD.

METHODS

Patients. Postmenopausal women (17-beta-estradiol <100 pmol/liter and follicular stimulating hormone [FSH] >40 IU) with stable exertional angina (16), reproducible positive exercise tests for myocardial ischemia, angiographically proven CAD (defined as at least 70% narrowing of the lumen diameter in one or more of the major coronary arteries or their major branches) and/or previous myocardial infarction were enrolled. No patient had a myocardial infarction in the previous six months. Patients who had taken hormone therapy in the previous three months, were taking digoxin, had abnormal left ventricular function or had resting electrocardiographic (ECG) conduction abnormalities were excluded. The study was undertaken at two sites; therefore, the protocol was approved by the respective institutional Ethics Committee. All patients gave written, informed consent.

Study design. One week before commencing the study, all anti-anginal medications other than sublingual nitroglycerin were withdrawn for the duration of the study. Sublingual nitroglycerin and caffeine-containing foods were prohibited for 3 h before each exercise test.

Patients performed a screening treadmill exercise test according to the modified Bruce protocol. Patients with a positive test for myocardial ischemia (ST segment depression ≥1 mm) then commenced a single-blind phase of 17-beta-estradiol (Estrace, Bristol Myers Squibb, Princeton, New Jersey) for four weeks (1 mg/day for 18 days followed by 2 mg/day for 10 days). Estradiol (2 mg/day) was then continued for the duration of the study. At the end of the fourth week, patients were randomized, in double-blinded manner, for 12 days to either oral MPA (10 mg/day) and transvaginal progesterone gel placebo or MPA placebo and active transvaginal progesterone gel (90 mg every other day; Crinone, Columbia Laboratories; Paris, France). After another 16 days on estradiol alone, the patients crossed over to progestin treatment and repeated the protocol on the opposite treatment regimen. Exercise testing was performed after each estradiol phase and on day 10 of each progestin phase (Fig. 1). Study drug compliance was checked by a drug count at the end of each treatment phase.

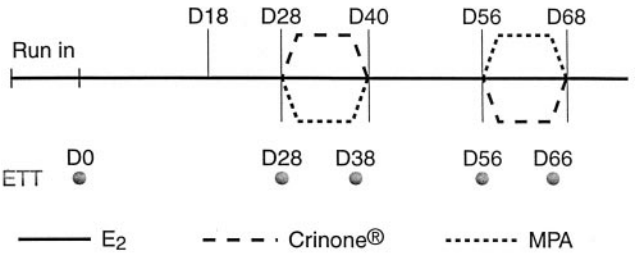

Figure 1. Flow chart of the study design. Anti-anginal medications were stopped during the run-in phase. Patients were assigned single-blind 17-beta-estradiol (E_2; 1 mg/day). On day 18 (D18), this was increased to 2 mg/day and continued for the remainder of the study. Randomization to vaginal progesterone gel (Crinone) or MPA occurred on day 28 (D28) and day 56 (D56). Exercise treadmill testing (ETT) was performed on day 0 (D0), D28, D38, D56 and D66. **Long-dashed line** = Crinone; **short-dashed line** = MPA.

Hormone levels. A venous blood sample for measurement of plasma levels of 17-beta-estradiol, progesterone and FSH was taken immediately before the first screening exercise test and before each test of the single-blind and double-blind phases. Plasma was frozen and analyzed by chemiluminescence (Chiron Diagnostics) at a core laboratory to avoid knowledge of the study treatment.

Exercise testing. Exercise tests were performed using a Marquette CASE-15 computer-assisted recorder system. An averaged 12-lead ECG was obtained at rest, every minute during exercise, at the onset of anginal symptoms, at the onset of 1-mm ST segment depression, at peak exercise and every minute during recovery. Leads II, V_2 and V_5 were continuously monitored. To accurately capture the time to the onset of 1-mm ST segment depression, the investigator initiated the printing of ECGs as the change from baseline ST-segment to 1-mm ST segment depression approached, and continued recording until the ST segment depression decreased beyond 1 mm. Systolic and diastolic blood pressures were measured at rest, at the end of each stage during exercise and every 2 min during recovery.

A positive ECG response was defined as horizontal or downsloping ST segment depression ≥1 mm at 60 ms after the J point (17) occurring in at least two contiguous leads and at least six consecutive complexes. Exercise tests were concluded at the point of physical exhaustion, ST segment depression ≥3 mm, severe angina, severe dyspnea or a decline in systolic blood pressure >20 mm Hg. Total exercise time, time to 1-mm ST segment depression, heart rate and blood pressure at the onset of 1-mm ST segment depression and peak exercise, maximal ST segment depression and time to development of angina during exercise were recorded. The rate–pressure product was calculated as the product of heart rate and systolic blood pressure.

Exercise ECGs were analyzed by an experienced independent investigator who was unaware of the clinical data.

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Table 1. Patient Characteristics (n = 18)

Age (yrs)	59 ± 7
Time since onset of angina (yrs)	3.5 ± 2.4
Hypertension	9
Non–insulin-dependent diabetes mellitus	2
Hypercholesterolemia	4
Previous myocardial infarction	8
Coronary artery disease	
One vessel	4
Two vessels	9
Three vessels	5
Time since menopause (yrs)	12 ± 6
Total cholesterol (mmol/liter)	6.7 ± 1.1

Data are presented as the mean value ± SD or number of patients.

Table 2. Hormone Profile After Each Treatment Period

Hormone	Baseline	E1	E+P	E+MPA
17-beta-estradiol (pg/ml)	26 (21–33)	76* (60–95)	97* (77–122)	87* (69–109)
Progesterone (ng/ml)	0.25 (0.16–0.40)	0.27 (0.17–0.43)	0.89* (0.57–1.41)	0.26 (0.16–0.41)
FSH (IU/liter)	55 (44–69)	26* (21–32)	17* (13–21)	14* (12–18)

*$p < 0.001$ compared with baseline. Data are presented as the geometric mean value (95% confidence interval).

E1 = single-blind estradiol phase; E + P = estradiol plus progesterone phase; E + MPA = estradiol plus medroxyprogesterone acetate phase; FSH = follicular stimulating hormone.

The ECG lead showing the greatest ST segment depression in the screening exercise tests was selected for analysis.

Statistical analysis. Analysis of variance was used for the main analysis, with treatment, period and dose as fixed variables, and patient and period within the patient as random variables. The prestudy baseline values were considered as a covariate and were included in the analysis of variance as such. A significant treatment–period interaction was indicative of a carry-over effect. Validity checks were made using the Anderson-Darling statistic, Cramer von Mises statistic, Watson statistic and Bartlett's test. Data were log-transformed when the assumption of equal variances was not met (baseline and peak blood pressures and hormone profile data only). These data are expressed as the geometric mean value (95% confidence interval [CI]). All other exercise data are expressed as the mean value (95% CI). Demographic data are expressed as the mean value ± SD. For the hormone profiles, each treatment mean value was compared with the baseline mean value, and the Bonferroni procedure was used to adjust the p values for multiple comparisons. p values ≤ 0.05 were considered to be statistically significant.

RESULTS

Patients. Twenty-six patients were enrolled. Two patients were withdrawn due to unstable angina shortly after commencing MPA treatment in combination with estrogen. One patient withdrew while taking combination estrogen and transvaginal progesterone gel due to heavy vaginal bleeding, which ceased two days after stopping treatment, and one patient withdrew because of severe breast tenderness after commencing the estrogen-only phase. One patient who was above the upper age limit was inadvertently randomized but did not start treatment, one patient withdrew after a car accident and two patients dropped out for unspecified personal reasons. Therefore, 18 women completed the study (Table 1). Eight patients had a previous myocardial infarction and one had previous coronary artery bypass graft surgery. Four patients had a history of hyperlipidemia (range for all patients: 5.4 to 9.2 mmol/liter) and three of these patients were taking lipid-lowering medication. All patients had clinical and biochemical evidence of postmenopausal status (Table 2).

Hormone levels. Baseline hormonal levels confirmed the menopausal status of the participating subjects (Table 2). Estrogen treatment raised plasma 17-beta-estradiol ($p < 0.001$) and lowered FSH ($p < 0.001$) (Table 2). Cyclical treatment with MPA or vaginal progesterone further lowered plasma FSH (both $p < 0.001$) (Table 2). Plasma progesterone increased compared with baseline when women received progesterone gel ($p < 0.001$) (Table 2). The amplitude of this elevation is concordant with the subphysiologic levels of progesterone achieved with the vaginal gel (18). Plasma progesterone levels, however, were not different from baseline levels when receiving MPA (a molecule not readily measurable). This confirms the lack of cross-reactivity of the progesterone antibody with MPA. The decrease in plasma FSH after MPA treatment provides an indirect reflection of treatment compliance.

Exercise testing. Estradiol alone increased the time to 1-mm ST segment depression, as compared with baseline ($p < 0.001$) (Table 3 and Fig. 2). There was a significant increase in exercise time to the onset of 1-mm ST segment depression by combination estradiol/progesterone as compared with combination estradiol/MPA (Table 3 and Fig. 2), with a mean difference of 92 s (95% CI 35 to 149) ($p < 0.001$). Nine patients demonstrated at least 1-mm ST segment depression after taking progesterone, and 11 patients demonstrated at least 1-mm ST segment depression after taking MPA. Five patients had a negative exercise test for myocardial ischemia after taking both combination progesterone *and* combination MPA. For analysis, total exercise time was substituted for time to 1-mm ST segment depression in patients who did not reach 1-mm ST segment depression with treatment. There were no differences between the measured exercise variables after the first and second estrogen-alone phases.

There was a trend toward an increase in total exercise time by combination progesterone therapy as compared with combination MPA therapy (mean difference 31 s (95% CI 7 to 68) ($p = 0.083$) (Table 3). The rate–pressure product at rest, but not at 1-mm ST segment depression or peak exercise, was significantly decreased after combination progesterone therapy, as compared with after combination

Table 3. Effects of Estrogen Alone and Combined Therapy With Medroxyprogesterone Acetate and Progesterone at Rest and During Exercise

	Baseline	E1	p Value	E + P	E + MPA	p Value
Rest						
Heart rate (beats/min)	85 (78–91)	86 (77–95)	0.71	77 (73–81)	82 (79–86)	0.058
Systolic blood pressure (mm Hg)	146 (133–160)	145 (132–158)	0.76	137 (132–142)	140 (135–145)	0.403
Rate–pressure product (mm Hg × beats/min)	12464 (10,829–14,099)	12517 (10,476–14,559)	0.93	10470 (9,924–11,040)	11300 (10,720–11,920)	0.038
1-mm ST segment depression						
Heart rate (beats/min)	132 (121–142)	133 (121–145)	0.77	126 (121–132)	129 (123–135)	0.527
Systolic blood pressure (mm Hg)	173 (160–185)	177 (166–188)	0.49	181 (171–191)	175 (166–185)	0.403
Rate–pressure product (mm Hg × beats/min)	22965 (20,868–25,062)	23647 (20,878–26,416)	0.64	23440 (21,650–25,230)	22630 (20,840–24,420)	0.527
Time (s)	288 (204–371)	360 (266–453)	< 0.001	457 (417–497)	365 (324–405)	< 0.001
Peak exercise						
Heart rate (beats/min)	143 (134–153)	142 (132–152)	0.71	137 (130–143)	139 (133–146)	0.527
Systolic blood pressure (mm Hg)	184 (172–197)	194 (183–205)	0.15	181 (173–189)	187 (179–196)	0.254
Rate–pressure product (mm Hg × beats/min)	26278 (24,421–28,134)	27618 (25,065–30,170)	0.3	25270 (23,100–27,440)	26620 (24,450–28,790)	0.343
Time (s)	410 (310–510)	422 (330–513)	0.54	482 (456–509)	451 (425–478)	0.083

Data are presented as the mean value (95% confidence interval).
E1 = single-blind estradiol phase; E + MPA = estradiol plus medroxyprogesterone acetate; E + P = estradiol plus progesterone.

MPA therapy (mean difference 0.926 [95% CI 0.859 to 0.998]) (p = 0.038). Treatment with combination MPA tended to increase the rest heart rate as compared with combination progesterone therapy (mean difference 5 beats/min [95% CI 0.31 to 11]) (p = 0.058), but there was no difference in the heart rate at 1-mm ST segment depression or peak exercise. There was no difference in systolic blood pressure between the treatment regimens. Treatment–period interactions did not occur, indicating no carry-over effect for any variable, and no training effect was shown.

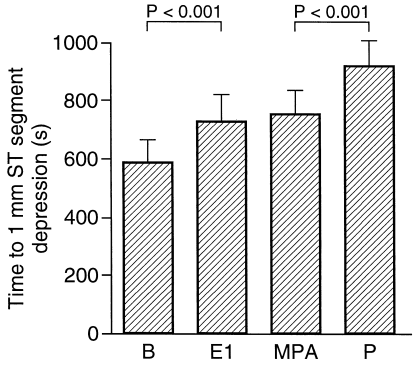

Figure 2. Effects of 17-beta-estradiol treatment alone (E1) and in combination with progesterone gel (P) or MPA on exercise time to the onset of 1-mm ST segment depression. Data are presented as the mean value ± SEM.

DISCUSSION

Findings and comparison with previous studies. Our results demonstrate that natural progesterone gel, when added to estradiol treatment, results in an increase in exercise time to myocardial ischemia compared with estrogen alone. In contrast, oral MPA has no effect on exercise time to myocardial ischemia in patients already taking estrogen. It has previously been demonstrated that both short-term (4,6) and long-term (5) estrogen therapy can delay the onset of signs of myocardial ischemia on the ECG and increase exercise tolerance. The results of the present study indicate a synergistic effect of estrogen and progesterone, but not estrogen and MPA, on exercise time to myocardial ischemia. This is a novel finding in the setting of CAD.

Similar to the findings of the long-term estrogen study by Webb et al. (5), we found no significant effect of either combined hormone regimen on total exercise time in the present study. However, there was a trend toward an increase in total exercise time by combination progesterone therapy as compared with combination MPA therapy (p = 0.083). Studies of conventional anti-anginal therapy, such as verapamil, have also shown a significant effect on the time to onset of signs of myocardial ischemia, but no effect on total exercise time (19).

Two patients (11%) developed unstable angina shortly after commencing the MPA treatment phase (two and five days) and were withdrawn from the study. These patients

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were successfully managed medically, then one went on to have percutaneous transluminal coronary angioplasty. Unstable angina is the result of complex pathophysiology that includes vasoconstriction, atherosclerotic plaque rupture and platelet-induced thrombosis (20). An MPA-induced tendency toward coronary vasoconstriction at the site of atheroma is one possible explanation for the development of unstable angina in these patients (14). The other possibility is that MPA results in an increased thrombotic tendency, although animal data suggest that this is unlikely (10).

Potential mechanisms. The observed significant increase in time to myocardial ischemia after combination estrogen plus progesterone gel could involve a number of mechanisms. Progesterone may have a synergistic effect with estrogen, however arguing against this is the very small measured increase in plasma concentration of progesterone with transvaginal progesterone gel. Another hypothesized mechanism may be that because the plasma levels of progesterone were so low, our observed increase in exercise time was purely due to an unopposed effect of a further 12 days of estrogen therapy. As MPA has been shown in animal models to oppose the beneficial vascular effects of estrogen, in the present study, MPA may be nullifying a potential further beneficial effect of more prolonged estrogen exposure on myocardial ischemia. For example, we have shown a further increase in the time to onset of myocardial ischemia after eight weeks of estrogen therapy as compared with four weeks (5). However, we showed no difference in measured exercise variables between the first and second estrogen-alone phases.

Effects of combination hormone therapy on vascular reactivity. Epidemiologic data suggesting a beneficial effect of postmenopausal hormone therapy on CAD risk are largely based on studies using unopposed estrogen; however, combination estrogen/progestin therapy is required to decrease the risk of endometrial hyperplasia and subsequent uterine carcinoma. One of the major unanswered questions in hormone replacement therapy for hypoestrogenic women is how to balance estrogen with progestin. This becomes more important in patients with CAD in whom changes in vasomotion may be detrimental. It is also particularly pertinent because the recent HERS study reported that continuous, combined, oral, conjugated equine estrogen plus oral MPA did not reduce the overall rate of CAD events in postmenopausal women with established CAD (3). In the early phase of HERS, there was an increase in CAD events in patients taking hormone therapy, specifically an increase in nonfatal myocardial infarction during the first year (first few months) of starting therapy. The survival curves then converged after one year and diverged during the second year to show a protective effect of hormone therapy in the latter years of the study. Although the patients in the present study and HERS were similar—namely, postmenopausal women with existing coronary atherosclerosis—exercise-induced myocardial ischemia is a measure of fixed disease in our study, as compared with the end point of cardiovascular events in HERS. Also, different estrogens were used: HERS used a continuous, combined preparation, whereas a cyclical regimen was used in the present study.

It is possible that MPA may oppose the vasodilator actions of estrogen, as has been demonstrated in animal models (21). Miyagawa et al. (14) studied the effect of physiologic levels of 17-beta-estradiol combined with MPA or progesterone on coronary vasomotion in ovariectomized rhesus monkeys. Coronary vasospasm was demonstrated in response to physiologic stimulation without injury when the animals were treated with MPA plus estradiol, but not when treated with progesterone plus estradiol. This latter combination protected against acetylcholine-induced vasospasm. These investigators concluded that MPA, in contrast to progesterone, increases the risk of coronary vasospasm. This finding concurs with our findings in that two patients were withdrawn from the study because of unstable angina after the initiation of the MPA phase of the study.

Effects of combination hormone therapy on atherosclerosis. In addition to its effect on vasomotor tone, MPA antagonizes the inhibitory effects of conjugated equine estrogens on coronary atherosclerosis in cynomolgus monkeys (10) and of 17-beta-estradiol in the rat carotid artery. This may be at least partially due to an inhibitory effect of MPA on the beneficial lipid effects of estrogen. In the Postmenopausal Estrogen-Progestin Interventions (PEPI) trial, MPA partially inhibited the estrogen-associated increase in HDL cholesterol more than micronized progesterone (22). However observational studies have shown a similar reduction in coronary heart disease risk in women using MPA plus estrogen as in women taking unopposed estrogen (23). There are a number of reports that clearly show a detrimental effect of MPA on the beneficial effects of conjugated equine estrogens with regard to atheroma development (10,11) and vascular reactivity (14,21). There are also studies showing that progesterone does not appear to have this inhibitory effect either on atheroma development (8,24) or vascular reactivity in animal models (14,15), nor on vascular reactivity in humans (25). Progesterone has an anti-smooth muscle proliferative effect in vitro (26), a feature that may be important in that atherosclerotic plaques of women who have suffered acute sudden death have more smooth muscle cell proliferation than male subjects (27).

Study limitations. The present study was designed to investigate whether the addition of progestins in women taking estrogen affects the anti-ischemic properties of estrogen. The design might have included a progestin placebo-placebo arm or might have given the estradiol in a double-blind, placebo-controlled fashion. However, this would have added to the already complex design of the study and may not have contributed any further to the current knowledge in this field. Indeed, previous randomized, placebo-controlled studies have reported effects of estrogen alone on myocardial ischemia (4–6).

Conclusions. Both the present study and HERS argue that the choice of progestin may be important in higher risk

women with established CAD. The choice of natural progesterone in this group of patients would seem more appropriate, as natural progesterone gel enhances the effects of estrogen on exercise-induced myocardial ischemia. Further randomized studies investigating different estrogens and progestins, as well as doses and routes of administration in different patient groups, will be required before definitive conclusions can be made about the use of hormone therapy in postmenopausal women who have, or are at increased risk of having, cardiovascular disease.

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REFERENCES

1. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. Prev Med 1991;20:47–63.
2. Grodstein F, Stampfer MJ, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. N Engl J Med 1996;335:453–61.
3. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280:605–12.
4. Rosano GMC, Sarrel PM, Poole-Wilson PA, Collins P. Beneficial effect of oestrogen on exercise-induced myocardial ischaemia in women with coronary artery disease. Lancet 1993;342:133–6.
5. Webb CM, Rosano GMC, Collins P. Oestrogen improves exercise-induced myocardial ischaemia in women. Lancet 1998;351:1556–7.
6. Alpaslan M, Shimokawa H, Kuroiwa-Matsumoto M, Harasawa Y, Takeshita A. Short-term estrogen administration ameliorates dobutamine-induced myocardial ischemia in postmenopausal women with coronary artery disease. J Am Coll Cardiol 1997;30:1466–71.
7. Rosano GMC, Caixeta AM, Chierchia SL, et al. Acute anti-ischemic effect of estradiol-17 in postmenopausal women with coronary artery disease. Circulation 1997;96:2837–41.
8. Adams MR, Kaplan JR, Manuck SB, et al. Inhibition of coronary artery atherosclerosis by 17-beta-estradiol in ovariectomized monkeys: lack of an effect of added progesterone. Arteriosclerosis 1990;10:1051–7.
9. Gruchow HW, Anderson AJ, Barboriak JJ, Sobocinski KA. Postmenopausal use of estrogen and occlusion of coronary arteries. Am Heart J 1988;115:954–63.
10. Bellinger DA, Williams JK, Adams MR, Honore EK, Bender DE. Oral contraceptives and hormone replacement therapy do not increase the incidence of arterial thrombosis in a nonhuman primate model. Arterioscler Thromb Vasc Biol 1998;18:92–9.
11. Levine RL, Chen SJ, Durand J, Chen YF, Oparil S. Medroxyprogesterone attenuates estrogen-mediated inhibition of neointima formation after balloon injury of the rat carotid artery. Circulation 1996;94:2221–7.
12. Williams JK, Adams MR, Herrington DM, Clarkson TB. Short-term administration of estrogen and vascular responses of atherosclerotic coronary arteries. J Am Coll Cardiol 1992;20:452–7.
13. Williams JK, Adams MR, Klopfenstein HS. Estrogen modulates responses of atherosclerotic coronary arteries. Circulation 1990;81:1680–7.
14. Miyagawa K, Rosch J, Stanczyk F, Hermsmeyer K. Medroxyprogesterone interferes with ovarian steroid protection against coronary vasospasm. Nat Med 1997;3:324–7.
15. Jiang C, Sarrel PM, Lindsay DC, Poole-Wilson PA, Collins P. Progesterone induces endothelium-independent relaxation of rabbit coronary artery in vitro. Eur J Pharmacol 1992;211:163–7.
16. Gibbons RJ, Chatterjee K, Daley J, et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Chronic Stable Angina). Circulation 1999;99:2829–48.
17. Simoons ML. Optimal measurements for detection of coronary artery disease by exercise electrocardiography. Comp Biomed Res 1977;10:483–99.
18. Fanchin R, de Ziegler D, Bergeron C, Righini C, Torrisi C, Frydman R. Transvaginal administration of progesterone. Obstet Gynecol 1997;90:396–401.
19. Livesley B, Catley PF, Campbell RC, Oram S. Double-blind evaluation of verapamil, propranolol, and isosorbide dinitrate against a placebo in the treatment of angina pectoris. BMJ 1973;17:375–8.
20. Davies MJ, Thomas AC. Plaque fissuring: the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. Br Heart J 1985;53:363–73.
21. Williams JK, Honore EK, Washburn SA, Clarkson TB. Effects of hormone replacement therapy on reactivity of atherosclerotic coronary arteries in cynomolgus monkeys. J Am Coll Cardiol 1994;24:1757–61.
22. The Postmenopausal Estrogen/Progestin Interventions Trial Writing Group. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. JAMA 1995;273:199–208.
23. Psaty BM, Heckbert SR, Atkins D, et al. The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women. Arch Intern Med 1994;154:1333–9.
24. Register TC, Adams MR, Golden DL, Clarkson TB. Conjugated equine estrogen alone, but not in combination with medroxyprogesterone acetate, inhibits aortic connective tissue remodeling after plasma lipid lowering in female monkeys. Arterioscler Thromb Vasc Biol 1998;18:1164–71.
25. Gerhard M, Walsh BW, Tawakol A, et al. Estradiol therapy combined with progesterone and endothelium-dependent vasodilation in postmenopausal women. Circulation 1998;98:1158–63.
26. Lee W-S, Harder JA, Yoshizumi M, Lee M-E, Haber E. Progesterone inhibits arterial smooth muscle cell proliferation. Nat Med 1997;3:1005–8.
27. Burke AP, Farb A, Malcom GT, Liang Y-H, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med 1997;336:1276–82.