

Does angina vary with the menstrual cycle in women with premenopausal coronary artery disease?

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Abstract

Objective—To determine whether angina in women with established coronary heart disease varies with changes in hormone concentrations during the menstrual cycle.

Design—Subjects were prospectively studied once a week for four weeks.

Setting—Cardiology outpatient department of tertiary referral centre.

Subjects—Nine premenopausal women, mean (SEM) age 38.89 (2.18) years, with established coronary heart disease, symptomatic angina, and a positive exercise test.

Main outcome measure—Myocardial ischaemia as determined by time to 1 mm ST depression during symptom limited exercise testing. Position in the menstrual cycle was established from hormone concentrations.

Results—The early follicular phase, when oestradiol and progesterone concentrations were both low, was associated with the worst exercise performance in terms of time to onset of myocardial ischaemia, at 290 (79) seconds; the best performance (418 (71) seconds) was when oestrogen concentrations were highest in the mid-cycle ($p < 0.05$). Similar trends were observed in other measured variables. Progesterone concentrations did not influence exercise performance.

Conclusions—During the menstrual cycle myocardial ischaemia was more easily induced when oestrogen concentrations were low. This may be important for timing the assessment and evaluating treatment in women with coronary heart disease.

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Keywords: myocardial ischaemia; exercise testing; oestradiol; progesterone

The vascular effects of 17- β oestradiol may be important in the presence of myocardial ischaemia. Oestradiol appears to act as a vasodilator. Various mechanisms have been proposed for this, including restoration of impaired endothelial function,¹ calcium antagonism,² alterations in sympathetic tone,³ and angiotensin converting enzyme inhibition.⁴ Several investigators have attempted to show an antianginal effect of postmenopausal oestrogen replacement treatment, but with mixed results.^{5–7}

Coronary heart disease is rare before the menopause, partly owing to the protective effect of female sex hormones. There are, however, important physiological changes related to cyclical fluctuations in oestradiol that effect vascular tone.^{8,9} Furthermore, during the different phases of the menstrual cycle variance in the severity of several conditions—including migraine,¹⁰ asthma,¹¹ and cardiac arrhythmias¹²—is well documented. In one case report, pronounced manifestations of ischaemic heart disease associated with vasospasm were noted, with variation in the menstrual cycle, and it has been suggested that angina in the absence of obstructive coronary disease (syndrome X) is also affected by the menstrual cycle.¹³ In order to clarify the role of the different female hormones in patients with angina and angiographically documented coronary artery disease, we investigated the effect of menstrual periodicity on the severity of angina and exercise performance using the exercise treadmill ECG.

Methods

We examined women who were premenopausal, with regular monthly menses and a follicular stimulating hormone (FSH) concentration < 13 U/l and luteinising hormone (LH) < 43 U/l on all four visits. Inclusion criteria were the presence of angiographically significant coronary heart disease ($> 50\%$ diameter stenosis), symptomatic angina, and a positive exercise test. Patients taking oral contraceptives or who were pregnant were excluded, as were women with ECG abnormalities (left bundle branch block, left ventricular hypertrophy, or digoxin treatment), which would make interpretation of the treadmill ECG unreliable. Women were randomly started on the trial protocol irrespective of their position in the menstrual cycle. Before each exercise test blood was drawn for oestradiol, progesterone, LH, and FSH. Antianginal treatment was left unchanged throughout the study.

Exercise treadmill testing was performed using a Marquette MAX I apparatus (Marquette Medical Systems, Milwaukee, USA) with automatic signal averaging of ST segments. We used the symptom limited Bruce protocol. Blood pressure was measured at one minute intervals. ST segment depression was considered to be significant if there was 1 mm of planar or downsloping ST depression in any two consecutive leads lasting for 10 or more beats. The same leads with initial ST depression were used for each subsequent evaluation. Two experienced investigators who were unaware of the menstrual or symptomatic status of the

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subject reported the exercise test. The exercise test was repeated at the same time of day in the same ambient conditions on four consecutive weeks. The study was approved by the local ethics committee, and all patients gave their written consent.

No formal power calculation was performed because of the lack of previous work in the area; however, a target population of 10 patients was envisaged from the work with postmenopausal oestrogen in women with angina.⁵ The population was then subdivided according to the phase in the menstrual cycle (early follicular, late follicular, early luteal, late luteal). Position in the menstrual cycle was defined as weeks from the early follicular phase (low oestrogen, low progesterone) and confirmed by appropriate hormone concentrations at each of the other visits.

Data were analysed using the SPSS for windows statistical package. Data are presented as mean (SEM). Two way comparisons were performed using paired or unpaired *t* tests as appropriate. Group trends were assessed using analysis of variance for repeated measures. All data fulfilled parametric assumptions as defined by Levine's test. Probability values of $p \leq 0.05$ were considered significant.

Results

RECRUITMENT

Twelve patients were initially recruited. Two had hormone concentrations which were in the postmenopausal range at one of the four visits and were therefore excluded. One patient, although showing ST depression during a preliminary exercise test, failed to show any abnormalities on tests during the trial period and so was also excluded. This woman also had an ejection fraction of less than 25%.

CHARACTERISTICS

The other nine patients were aged 38.89 (2.18) years. Four of the women had suffered a previous myocardial infarct and one had undergone coronary artery bypass surgery. Three patients were taking glyceryl trinitrate preparation, seven were taking lipid lowering treatment, two were on calcium antagonists, and five were on β blockers. Three subjects had three vessel disease, two had two vessel disease, and four had one vessel disease. All had good left ventricular function with an ejection fraction greater than 50%. One patient was diabetic and was on insulin, two had been classified as hypercholesterolaemic, and eight had been former smokers. Two patients entered the study during the early follicular phase, one in the late follicular phase, three in the early luteal phase, and two in the late luteal phase. No training effect between visits 1 and 4 was observed for time to ST segment depression, time to chest pain, or total exercise time. In the early follicular phase all subjects had low oestrogen and progesterone, while in the late luteal phase only one patient had a progesterone of less than 5 pmol/l and this patient had been luteal in the preceding week. All the other patients were appropriately in phase.

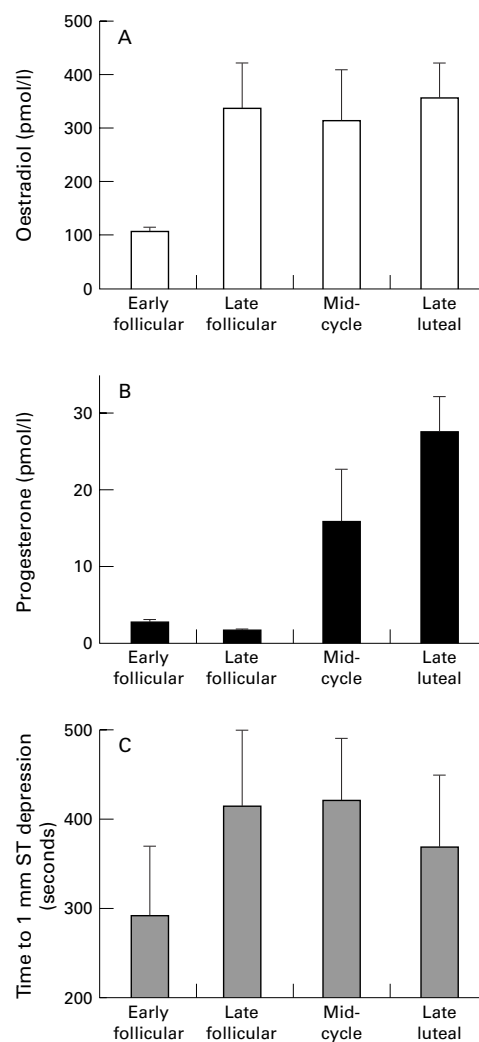


Figure 1 (A) Oestradiol (pmol/l); (B) progesterone (pmol/l); (C) time to 1 mm ST depression (with SEM) for each of the four phases of the menstrual cycle.

WEEK BY WEEK VARIATION

When the study period was divided into its constituent weekly visits, there was a significant effect of the different phases of the menstrual cycle on the onset of myocardial ischaemia, as assessed by time to 1 mm ST segment depression (fig 1). During the period when oestrogen concentrations were lowest (early follicular), the time to ST depression was also at its lowest and it was significantly lower than in the late follicular period and in mid-cycle visits when oestradiol concentrations were higher (table 1). Total exercise time and time to onset of angina were highest in the late luteal phase when both oestradiol and progesterone concentrations were high, but although these differences were significant in pairwise comparisons, neither reached overall significance. Similar non-significant trends were observed in the maximum depth of ST segment depression. Examining the haemodynamic performance on the treadmill, the double product of systolic blood pressure and heart rate at the onset of myocardial ischaemia was also higher in the late follicular and mid-cycle visits, although again overall this did not reach significance.

Table 1 Results of exercise treadmill testing for each phase of the menstrual cycle

	Oestradiol (pmol/l)	Progesterone (pmol/l)	Double product at 1 mm ST depression	1 mm ST depression (s)	Angina (s)	Exercise time (s)	ST depth (mm)
Early follicular	104.6 (11.5)	2.5 (0.6)	18 281 (1880)	290 (79)	379 (82)	453 (75)	1.9 (0.3)
Late follicular	335.7 (82.3)*	1.5 (0.2)	21 108 (1364)	412 (87)*	397 (56)	485 (69)	1.4 (0.2)
Mid-cycle	313.0 (89.6)*	15.7 (7.0)	21 565 (1696)*	418 (71)*	409 (69)	524 (56)	1.3 (0.3)
Late luteal	352.5 (66.2)*	27.4 (4.7)*	18 261 (2045)	366 (82)	487 (81)**	488 (74)*	1.5 (0.2)*
ANOVA	0.08	0.07	0.18	0.02	0.17	0.27	0.20

Values are mean (SEM).

* $p < 0.05$, ** $p < 0.01$ v early follicular phase.

ANOVA, analysis of variance.

Table 2 Results for the 18 exercise tests performed in follicular and luteal phases (two tests per patient per phase)

Variable	Phase	Mean (SEM)	<i>p</i> Value
Oestradiol (pmol/l)	Follicular	206 (46)	0.08
	Luteal	334 (53)	
Progesterone (pmol/l)	Follicular	2 (0.4)	< 0.01
	Luteal	22 (4)	
Rate-pressure product (1 mm ST) (beats/min/mm Hg)	Follicular	19 695 (1178)	0.90
	Luteal	19 913 (1350)	
Time to 1 mm ST depression (min)	Follicular	351 (60)	0.61
	Luteal	392 (53)	
Time to onset of chest pain (min)	Follicular	388 (48)	0.43
	Luteal	446 (52)	
Total exercise time (min)	Follicular	469 (49)	0.36
	Luteal	506 (45)	

LUTEAL VERSUS FOLLICULAR PHASE

Eighteen exercise tests in the nine patients were compared in both the luteal (high progesterone) and follicular (low progesterone) phases to explore the effect of progesterone on exercise performance. Time to onset of myocardial ischaemia, anginal chest pain, and total exercise time were not significantly different in either of these phases (table 2).

Discussion

It has been established that oestrogen and other female sex hormones have important effects on many different organ systems, including both the coronary and the peripheral arteries.^{14 15} The net result of oestrogen action is to cause vasodilatation, although this is antagonised to some extent by the progestin or progesterone.¹⁶ The mechanisms of this vasodilator effect have been examined in both *ex vivo* and *in vivo* models. Collins and colleagues showed that when oestradiol is injected into atheromatous human female coronary arteries, the atheromatous paradoxical constrictor effect in response to acetylcholine is reversed and the arteries dilate normally.¹⁴ This restoration of impaired endothelial function with augmentation of nitric oxide (NO) release from the endothelium is an important vasodilator reflex and will tend to increase coronary blood flow. Oestradiol at supraphysiological doses has also been noted to inhibit the influx of calcium ions into vascular smooth muscle cells, thus promoting vasodilatation,² although the significance of this *in vivo* is not yet clear. Other mechanisms of vasodilatation include modification of the activity of angiotensin converting enzyme inhibition⁴ and antagonism of the constrictor effects of endothelin 1.¹⁷

Several published studies have suggested that postmenopausal oestrogen replacement may have antianginal effects, at least at supraphysiological doses, but this has not been universally accepted. Certainly the loss of female sex hormones at the menopause appears to be associated with a higher risk of cardiovascular disease, as shown by the increased cardiac risk among women undergoing early oophorectomy and the subsequent attenuation of this risk with hormone replacement therapy.^{18 19} In a small case control study, premenopausal women with coronary disease had lower concentrations of oestradiol than healthy controls.²⁰

In premenopausal women it is already established that blood pressure varies in a cyclical manner with fluctuations in the menstrual cycle, the highest pressure being observed in the luteal phase.^{21 22} There is a particularly steep rise as menstruation approaches, after which there is a return to baseline values. The release of NO shows clear evidence of periodicity with the menstrual cycle. Kharitonov and colleagues found that normal subjects at mid-cycle exhaled twice as much NO as in the perimenstrual period.⁹ Based on this evidence we hypothesised that cyclical variation in sex hormone concentrations might bring about alterations in the severity of anginal symptoms.

Exercise performance is a balance between symptomatic ischaemia and perception of symptoms. Sex hormones not only appear to modulate coronary tone, but can also influence pain perception and mood. In the early follicular phase when both oestradiol and progesterone concentrations were low, overall performance on the treadmill was at its worst. Myocardial ischaemia as judged by ST depression was significantly improved between this visit and the subsequent visits when oestradiol concentrations were higher. Over the four visits there was a significant effect of the menstrual phase. Time to onset of chest pain was also least in the perimenstrual period, although this was not significant. Total exercise time was unaffected. However, this dissociation between ischaemic markers and overall exercise performance is well reported. The variation in time to onset of ST depression may represent a loss of oestrogen mediated anti-ischaemic effect but could also represent alterations in autonomic tone that could in turn affect electrical repolarisation. It has been reported that false positive exercise tests occur more often in oestrogen positive women (that is, premenopausal or among those taking hormone replacement therapy).²³ Similarly progesterone

has been reported to affect the interpretation of exercise tests.²⁴ In this study, when the population was divided into follicular (low progesterone) and luteal (high progesterone) phases no effect on treadmill performance was observed.

CONCLUSIONS

Our study is small in size and by its nature exploratory. The differences between the individual phases need to be interpreted with caution as there is some dissociation between clinical symptoms and treadmill derived ischaemia (this is particularly important because of the small sample size). Nevertheless the results suggest that myocardial ischaemia, as assessed on the treadmill, is worst in the perimenstrual period when both oestrogen and progesterone concentrations are at their lowest. This hypothesis of "menstrual angina" requires further evaluation and should be taken into account when interpreting symptoms and exercise tests in premenopausal women with angina.

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