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Sex hormone plasma levels in premenopausal women with coronary heart disease

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Abstract

Background: *Coronary heart disease (CHD) in premenopausal women is rare. This may be related to the protective effect of endogenous estrogens on the female cardiovascular system. The aim of the study was to analyse the levels of sex hormones in premenopausal women with CHD confirmed by coronary angiography.*

Methods: *Thirty women aged 34–53 years and with a mean age of 46.3 ± 5.2 years were enrolled in the study. All were regularly menstruating, in the premenopausal period (i.e. with FSH < 15 IU/L and FSH > LH), with stable CHD and with significant atherosclerotic plaques in coronary angiography (narrowings > 50% of the lumen diameter). Of these, 80% had myocardial infarction in their histories. Estradiol plasma levels and gonadotrophic hormone (luteinising hormone LH and follicle-stimulating hormone FSH) plasma levels were measured in the women under investigation.*

Results: *A diminished estradiol level was diagnosed in 14 patients (46.7%) of the 30 premenopausal women examined (patients with hypoestrogenemia). In 12 women (40%) hypoestrogenemia was accompanied by diminished levels of gonadotrophins (hypoestrogenaemia of hypothalamic origin).*

Conclusion: *The plasma estradiol level was diminished in 46.7% of premenopausal women with CHD. Insufficient level of endogenous estradiol could have contributed to the early development of atherosclerotic plaques in the epicardial coronary arteries of the women examined.*
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Key words: women, coronary heart disease, estradiol

Introduction

Diseases of the cardiovascular system are responsible for a majority of deaths and cause substantial morbidity among Polish women. According to statistical data, 57.1% of deaths in women above 25 years of age are caused by diseases of the heart and vessels [1, 2].

Coronary heart disease (CHD) is infrequently diagnosed in premenstrual women [1], what could be related to the protective influence of endogenous estrogens on the feminine cardiovascular system.

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Estrogens, through their membrane receptor (the non-genomic effect), stimulate the immediate release of nitrate oxide from endothelial cells, which results in vasodilatation [3]. Moreover, estrogens partially block type L calcium channels [4] and cause an opening of the potassium channels in the vascular smooth muscle cells [5], which also promotes vasodilatation. Estrogens, through their intracellular receptors, affect gene expression (the genomic effect). Through this mechanism they increase synthesis of nitric oxide and prostacycline as well as augment expression of the atrial natiuretic peptide (ANP) gene [6]. Furthermore, estrogens have a favourable effect on the plasma lipid profile by lowering the level of low-density lipoprotein cholesterol (LDL) through the up-regulation of their receptors, raising the level of high density lipoprotein cholesterol (HDL) and decreasing lipoprotein (a) level [7]. Estrogens lower the fibrinogen level and stimulate fibrinolysis by reducing plasminogen activator inhibitor-1 (PAI-1). They improve glucose metabolism and decrease serum insulin level [8]. Estrogens show antioxidant properties, accelerate endothelial cell regeneration after mechanical injury and improve endothelial function, which results in increased hyperaemic vasodilatation [8]. Estrogens decrease proliferation of the vascular smooth muscle cells and inhibit apoptosis of the endothelial cells [9]. Moreover, experimental data confirm the presence of estrogen receptors in the central nervous system in the nuclei of the autonomic nervous system and in the peripheral nerve endings [10] Estrogens increase synthesis and release of acetylcholine on every level of the autonomic nervous system and thus contribute to the relative predominance of the parasympathetic nervous system in women [10].

Little published work is available on sex hormone levels in menstruating women with CHD. The results of two papers indicate a lower estradiol level in premenopausal women with diagnosed CHD compared to healthy women [11, 12]. Other authors do not confirm this association [13, 14].

In view of the divergent results of the former papers we performed an analysis of the sex hormone levels in premenopausal women with angiographically proven CHD.

Methods

Thirty women aged 34–53 years and with a mean age of 46.3 ± 5.2 years were enrolled in the study. All were regularly menstruating, in the premenopausal period (i.e. with FSH < 15 IU/L and FSH > LH) and were hospitalized in the Department of Coronary Heart Disease of the Institute of Cardiology, Collegium Medicum Jagiellonian University and/or treated in the out-patient Cardiological Department of the John Paul II Hospital.

The inclusion criteria were as follows:

— stable CHD diagnosed on the basis of anamnesis, non-invasive tests and coronary angiography;
— the presence of significant atherosclerotic plaques (above 50% of the lumen diameter) in coronary angiography;
— informed consent to participation in the study.

Estradiol plasma level and gonadothrophic hormone (luteinising hormone LH and follicle-stimulating hormone FSH) plasma levels were measured in the women under investigation.

Estradiol, LH and FSH levels were measured with electrochemiluminescence immunoassay (ECLIA, Roche). Because of the proven functional amenorrhoea in menstruating women with CHD, measurements of the sex hormone levels were performed on any day of the menstrual cycle [12]. Hypoestrogenemia was diagnosed if the estradiol plasma level was below 50pg/ml and secondary hypoestrogenemia related to hypopituitarism was diagnosed where coexisting LH and FSH levels fell below 10mIU/ml (hypoestrogenemia of hypothalamic origin) [12].

Statistical analysis was performed using the STATISTICA for Windows software. Results were shown as mean ± 1 standard deviation (SD) for continuous data and proportions for categorical data. In order to evaluate the normality of the data distribution, the Shapiro-Wilk test was used. For normal data distribution a t test was used. When data distribution was not normal, non-parametric tests were used (the Wald-Wolfowitz test, the Mann-Whitney U test or the Kolmogorov-Smirnov test). A p value < 0.05 was considered statistically significant.

Results

Class III angina according to the CCS classification was the most frequently encountered form in the women examined, being observed in 15 patients (50%). Five women (16.7%) had class I angina and 10 patients (33.3%) had class II angina. Heart failure was found in 4 patients (13.3%). Heart failure class I according to NYHA classification was observed in 2 patients (6.7%), class II in 1 woman (3.3%) and class III also in 1 woman (3.3%).

Twenty four patients (80%) had history of myocardial infarction (MI). Fourteen patients (46.7%) had a Q-wave MI and 10 patients (33.3%)

had a non Q-wave MI. A majority of the patients (21 women, 70.0%) had had 1 MI, while 3 patients (10%) had had 2 MI.

Single-vessel disease was that most frequently encountered in the patients examined, being found in 21 women (70%). Double-vessel disease was diagnosed in 4 patients (13.3%) and triple-vessel disease was present in 5 women (16.7%).

Eighteen patients (60%) underwent revascularisation before enrolment to the study. Percutaneous transluminal coronary angioplasty was performed in 17 patients (56.7%). One woman underwent coronary artery by-pass graft surgery.

Plasma estradiol levels in the women examined ranged from 10.05 to 143.60 pg/ml, with a mean of 59.75 ± 15.86 pg/ml. LH plasma levels ranged from 1.01 to 13.04 mIU/ml, with a mean of 5.88 ± ± 6.11 mIU/ml. FSH plasma levels ranged from 2.30 to 14.03 mIU/ml, with a mean of 6.82 ± 6.83 mIU/ml.

On the basis of the above analyses hypoestrogenemia was diagnosed in 14 patients (46.7%). Twelve women (40%) had both hypoestrogenemia and diminished levels of gonadotrophins. These were patients with secondary hypoestrogenemia related to hypopituitarism (hypoestrogenemia of hypothalamic origin).

Discussion

Hypoestrogenemia was found in nearly half the examined premenopausal women with CHD. A diminished estradiol level was related to low gonadotrophin levels in 12 out of 14 women with hypoestrogenemia. These patients were diagnosed with hypoestrogenemia of hypothalamic origin.

Little published work is available which evaluates sex hormone levels in premenopausal women with CHD. The results of WISE (Women's Ischaemia Syndrome Evaluation) study indicate significantly lower estradiol and FSH levels in premenopausal women with significant atherosclerotic plaques in coronary angiography compared to premenopausal women with chest pain and normal coronary angiography [12]. Hypoestrogenemia of hypothalamic origin was found in 9 out of 13 women (70%) with CHD and critical atherosclerotic plaques in coronary angiography compared to 30% of women without coronary atherosclerosis [12]. Moreover, hypoestrogenemia of hypothalamic origin was an independent marker of critical narrowings in the epicardial coronary arteries in premenopausal women with chest pain [12]. Other works have demonstrated lower plasma estradiol levels in menstruating women with a history of MI compared to healthy women [11]. However, Malczewska et al. [13] found no significant differences in sex hormone levels in menstruating women with and without significant atherosclerotic plaques in coronary angiography.

Hypoestrogenemia leads to endothelial dysfunction. Hashimoto et al. [15] examined endothelial function in three phases of the menstrual cycle in healthy women and found endothelium-dependent vasodilatation to be greatest during the follicular and luteal phases of the menstrual cycle, those phases in which the level of estradiol is high [15]. Endothelial dysfunction was also found in postmenopausal women with CHD. Intracoronary infusion of acetylcholine to the atherosclerotic coronary arteries of postmenopausal women caused vasoconstriction [16]. Intracoronary administration of estradiol before infusion of acetylcholine normalised endothelial function and vasodilatation following acetylcholine infusion has been observed [16]. In other studies it was found that sublingual estradiol diminished the intensity of ischaemia in the exercise treadmill test in postmenopausal women with CHD [17]. Furthermore, the anti-atherosclerotic effect of estradiol has been demonstrated by experimental data. Oral estradiol supplementation delayed the development of atheroclerosis in castrated simian females fed with a cholesterol-rich diet [18].

Randomised prospective studies in postmenopausal women do not confirm the favourable effect of oral estradiol supplementation on the formation and progression of atherosclerotic plaques [19–21]. Only the results of EPAT (Estrogen in the Prevention of Atherosclerosis Trial) indicate that in postmenopausal women with elevated LDL-cholesterol levels the intima-media thickness of the common carotid artery decreases in patients on oral estradiol supplementation and increases in women receiving placebo [22].

Analysis of trials which evaluate the effect of oral estradiol supplementation in postmenopausal women necessitates consideration of the means by which estradiol is to be administered. The effect of endogenous estradiol or estradiol administered parenterally cannot be compared with oral estradiol supplementation [8]. Estradiol secreted in the ovaries or administered parenterally enters the systemic circulation directly. Estradiol administered orally through the portal circulation reaches the liver at a high concentration and is metabolised to inactive metabolites (the first-pass effect) [8]. The dose of orally administered estradiol required to obtain a physiological plasma estradiol level is 10 times higher than the equivalent dose of parenterally-

-administered estradiol [8]. These high estradiol levels influence the hepatic metabolism of other substances such as apolipoproteins, proteins of the coagulation system and C-reactive protein, which has a prothrombotic and proinflammatory effect with consecutive progression and destabilisation of the atherosclerotic plaques [8].

The results of this study indicate the high incidence of hypoestrogenemia in premenopausal women with stable CHD. Insufficient levels of endogenous estradiol may have contributed to the early development of atherosclerotic plaques in the epicardial coronary arteries of the women examined.

In conclusions, plasma estradiol levels were diminished in 46.7% of premenopausal women with coronary heart disease. Insufficient level of endogenous estradiol could have contributed to the early development of atherosclerotic plaques in the epicardial coronary arteries of the women under investigation.

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