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The genetic polymorphisms of vasoactive hormones and the echocardiographic parameters in women.

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ABSTRACT

This paper deals with the study of the genetic polymorphisms of vasoactive hormones and their relationship with echocardiographic indices in non-pregnant women and during gestation. The study group included 317 women: 241 pregnant (gestational age - 37-40 weeks) and 76 non-pregnant women. During echocardiographic study the size of the atria and ventricles of the heart were assessed. All women underwent typing of fourteen molecular genetic markers of vasoactive hormones. It was found that the molecular genetic markers -6A/G AGT, -1166A/C ATIIR1, I/D ACE are associated with echocardiographic indices in non-pregnant women.

Keywords: vasoactive hormone genes, echocardiographic indicators, pregnancy, renin-angiotensin-aldosterone system.

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INTRODUCTION

The study of changes in the functioning of the cardiovascular system in women during pregnancy and their determinants is an important medical problem, since pregnancy is one of the physiological conditions that requires long-term and fundamental restructuring of many functional systems due to the need to maintain homeostasis (Siliberto et al, 2007). Disturbances in the functioning of the cardiovascular system in pregnant women can lead to a reduction of compensatory functions of the fetus, the development of chronic intrauterine hypoxia and placental insufficiency (Sidorova, 2006). A number of papers have been devoted to the investigation of the genetic basis of changes in the cardiovascular system functioning in pregnant women (Roberts et al, 2004; Zafarmand et al, 2008; Reshetnikov et al, 2015). However, most studies aimed at identification of genes responsible for certain disturbances in the cardiovascular system in pregnant women have been conducted abroad (Mello et al, 2005).

MATERIALS AND METHODS

We have analyzed the survey results of 317 women: 241 pregnant women (gestational age of 37-40 weeks) and 76 non-pregnant women (average age - 27.98 ± 5.29 years (ranging 20-43 years). The sample included Russian individuals, who are natives of Central Black Soil region of Russia and have no relationship with each other.

Clinical-laboratory and instrumental examination was carried out on the basis of women's Perinatal Center of St. Joasaph Belgorod Regional Clinical Hospital.

Echocardiographic study of women was conducted in accordance with a standard echocardiographic study protocol (guidelines of American Society of Echocardiography - ASE, 1989). We evaluated the following structural and geometric and functional parameters in the B-mode through the left parasternal and apical approaches: left ventricular length in the systole and diastole (LV length, mm), end-diastolic dimension of the left ventricle (LV EDD, mm), end-systolic dimension of the left ventricle (LV ESD, mm), end-diastolic dimension of the right ventricle (RV EDD, mm), the left and right atrial dimensions (LA mm and PP, mm), the thickness of the interventricular septum (IVS, mm) and the rear wall of the left ventricle (LVRW, mm) in the diastole, the sectional area of the left ventricle in short axis in the systole and diastole (S LV, cm^2). The volume of the left ventricle was measured by the "area-length" method: end-diastolic volume (LV EDV, ml), end-systolic volume (LV ESV, ml). Stroke volume (LV SV, ml) and ejection fraction (EF, %) were also calculated.

All women underwent typing of three molecular genetic markers of vasoactive hormones, namely diallel gene loci of angiotensin-converting enzyme (I/D ACE), angiotensinogen (-6A/G AGT), and angiotensin II receptor type 1 (-1166A/C ATIIR1). The choice of these systems for the study is due to their possible association with the functioning of the cardiovascular system by virtue of the ability of the studied polymorphisms to modify the expression of the corresponding genes or to lead to changes in the structure of the encoded products (Kikuya et al, 2003).

As the material for the study we used 8-9 ml of venous blood taken from the cubital vein of a proband. A genomic DNA was isolated from peripheral blood by the method of phenol-chloroform extraction (Mathew, 1984).

The genotyping of DNA markers was performed by polymerase chain reaction of DNA synthesis, analysis of amplified fragment length polymorphism, restriction fragment length polymorphism, and real-time detection of TaqMan probes by PCR.

The formation of database and the statistical calculations were carried out using the "STATISTICA 6.0" program. During the study of the relationship of genetic polymorphisms with pathogenetically significant quantitative characters, the nature of the distribution of these characters was initially assessed using the Shapiro-Wilk test (Rebrova, 2006). It was found that the distribution of all the studied quantitative characters was not consistent with a normal distribution and, therefore, the median (Me) and interquartile range (Q25-Q75) was used for their description, and for comparative analysis - the Mann-Whitney test with Bonferroni corrections (Rebrova, 2006).

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RESULTS

The analysis of echocardiographic indicators depending on the genetic polymorphisms of vasoactive hormones in 76 non-pregnant women was conducted.

It was found that women with highly productive D allele (genotypes DD and ID) in their genotype have the median of cross-sectional area of the left ventricular along the short axis in the systole equal to 6.18 cm^2, which is statistically significant (p=0.04) and exceeds by 15.73% the same indicator in women with low productivity genotype II at this locus. Also, women with DD and ID markers also have higher values of end-systolic dimensions of the left ventricle (by 7.69%) and end-systolic volume of the left ventricle (by 20.83%) as compared with women with genotype II (p=0.03) (Table 1).

Table 1. Significant associations of genetic polymorphisms of vasoactive hormones with echocardiographic indicators in women, Me (Q25-Q75)

Indicators	Polymorphisms		p
	I/D ACE		
	DD and ID (n=59)	**II (n=17)**	
LV S syst, cm^2	6.18(5.28-7.04)	5.34(4.58-5.77)	0.04
LV ESD, mm	28.0(26.0-30.0)	26.0(24.0-27.0)	0.03
ESV, ml	29.0(24.0-34.0)	24.0(21.0-28.0)	0.03
	-6A/G AGT		
	-6AA and -6AG (n=54)	**-6GG (n=22)**	
LV S diast, cm^2	17.29(15.96-18.11)	15.24(14.57-17.32)	0.008
LV length diast, mm	6.9(6.8-7.0)	6.8(6.7-6.9)	0.007
LV length syst, mm	5.5(5.3-5.8)	5.3(5.2-5.7)	0.03
LV EDD, mm	47.0(45.0-48.0)	44.0(43.0-47.0)	0.01
LA, mm	30.0(28.0-32.0)	32.0(30.0-34.0)	0.05
RV EDD, mm	27.0(26.0-30.0)	29.5(27.0-32.0)	0.03
LV EDV, ml	102.0(93.0-108.0)	88.5(82.0-103.0)	0.007
SV, ml	71.0(66.0-75.0)	64.0(60.0-73.0)	0.05
LVMMI, g/m^2	92.6(80.0-101.4)	81.9(72.2-90.8)	0.02
	-1166A/C ATIIR1		
	-1166CC and -1166AC (n=37)	**-1166AA (n=39)**	
RA, mm	31.0(29.0-33.0)	30.0(27.0-31.0)	0.003
RV EDD, mm	29.0(27.0-31.0)	27.0(25.0-30.0)	0.01

The relationship was revealed between -6A/G AGT polymorphism with echocardiographic indices in women (Table 1).

We also revealed statistically (p=0.007-0.05) higher values of sectional area of the left ventricle along the short axis in the diastole (by 13.45%), the length of the left ventricle in the diastole (by 1.5%) and systole (by 3.8%), end-diastolic dimensions of the left ventricle (by 6.82%), end-diastolic (by 15.25%) and stroke volume (by 10.93%) and the left ventricular myocardium mass index (by 13.6%) in women with -6AA and -6AG AGT genotype as compared with individuals with -6GG AGT genotype.

During the study of the association of -1166A/C genetic polymorphism of the angiotensin II receptor type 1 with echocardiographic indicators in women we determined larger dimensions of right heart chambers (atria and ventricles) in women with -1166C allele (-1166CC and -1166AC genotype) as compared with homozygous for -1166A allele (p=0.003-0.01) (Table 1).

DISCUSSION

The results of the study of the associations of I/D ACE polymorphism with heart size in women have shown a slight decrease in the contractile function of the left ventricle in women with highly productive D allele (DD and ID genotype) at locus I/D ACE. Individuals with a molecular genetic marker DD have higher values of diastolic and mean arterial pressure as compared with women with genotype II, apparently, due to a high level of production of angiotensin converting enzyme, having vasoconstriction effect (Danser et al, 1995; Limborskaya et al, 2002). At the same time, an increased vascular tone in women of this group causes an increase in the afterload on the heart (increase in the residual volume of blood in the left ventricle during systole phase and decrease in stroke volume) (Strutinsky, Roytberg, 2003; Zatikyan, 2004) and the initial response from the heart to the process will be an increase in end-systolic volume and dimensions of the left ventricle, i.e. an ongoing decrease in systolic myocardial function. One can assume that the further marked increase in vascular tone in these individuals (e.g., in case of hypertension development) will cause both the formation and a significant increase in the afterload on the heart, which can lead ultimately to the development of left ventricular hypertrophy (Strutinsky, Roytberg, 2003).

Based on these data we can conclude that women with a highly productive -6A allele in their genotypes (-6AA and -6AG genotype) at polymorphism of -6A/G angiotensinogen, and individuals with -6GG genotype have certain morphological differences in the heart chambers. Another study determined the associations of -6AG AGT genotype with larger end-diastolic dimensions of the left ventricle in pregnant women with preeclampsia (Reshetnikov et al, 2009).

During the study of the association of -1166A/C genetic polymorphism of the angiotensin II receptor type 1 with echocardiographic indicators in women we determined larger dimensions of right heart chambers. Given that an increase in right heart occurs as a result of high blood pressure in the pulmonary circulation (Strutinsky, Roytberg, 2003) in the absence of the broncho-pulmonary pathology in the considered sample, we can assume some increase in vascular tone in the pulmonary circulation in the presence of -1166S allele of the angiotensin II receptor type 1 gene. Thus, the polymorphism may pose a further risk factor for pulmonary hypertension in women. In some studies, a genetic variant of -1166C ATIIR1 was found in hypertensive patients more often than in healthy ones (Kikuya et al, 2003; Jones et al, 2003; Hamidulaeva et al, 2007).

The evaluation of morphological and functional characteristics of heart in pregnant women (n=241) revealed no significant associations of genetic polymorphisms of vasoactive hormones with echocardiographic indicators. It should be noted at the same time that according to our previous findings, some of molecular genetic markers in non-pregnant period are associated with individual echocardiographic indices in women. At fertilization, when the short-term significant changes occur in the functioning of the female organism and its cardiovascular system, these associations level out (Sidorova, 2006; Siliberto et al, 2006; Sokolnikova, 2008).
Thus, the results of the study conducted the first time ever on a sample of Russian women born in the Central Black Soil Region of Russia have demonstrated the significant associations of polymorphic markers of the genes of vasoactive hormones with echocardiographic values.

REFERENCES

[1] Danser, A.H., Schalekamp, M.A., Bax, W.A., van den Brink, A.M., Saxena P.R., Riegger, G.A., Schunkert, H., 1995. Angiotensin-converting enzyme in the human heart. Effect of the deletion/insertion polymorphism. Circulation, 92(6): 1387-1388.

[2] Hamidulaeva G.A., Eliseeva M.R., Srozhidinova N.Z., Abdullaeva G.Zh., 2007. Distribution features of polymorphic markers of the renin-angiotensin-aldosterone system, the relationship with left ventricular hypertrophy in Uzbek patients with essential hypertension. Cardiology, 4: 54-58.

[3] Kikuya, M., Sugimoto, K., Katsuya, T., Suzuki, M., Sato, T., Funahashi, J., Katoh, R., Kazama, I., Michimata, M., Araki, T., Hozawa, A., Tsuji, I.,Ogihara, T., Yanagisawa, T., Imai, Y., Matsubara, M., 2003. A/C1166 gene polymorphism of the angiotensin II type 1 receptor (AT1) and ambulatory blood pressure: the Ohasama Study. Hypertens Res, 26(2): 141-145.

[4] Jones, A., Dhamrait, S.S., Payne, J.R., Hawe, E., Li, P., Toor, I.S., Luong, L., Wootton, P.T., Miller, G.J., Humphries, S.E., Montgomery, H.E., 2003. Genetic variants of angiotensin II receptors and cardiovascular risk in hypertension. Hypertension, 42(4): 500-506.

[5] Limborskaya S.A., Khusnutdinova E.K., Balanovskaia E.V., 2002. Ethnogenomics and genogeography of Eastern European nations. Moscow.

[6] Mathew, C.C., 1984. The isolation of high molecular weight eukaryotic DNA. Methods in Molecular Biology, 2: 31-34.

[7] Mello, G., Parretti, E., Fatini, C., Riviello, C., Gensini, F., Marchionni, M., Scarselli, G.F., Gensini, G.F., Abbate, R., 2005. Low-molecular-weight heparin lowers the recurrence rate of preeclampsia and restores the physiological vascular changes in angiotensin-converting enzyme DD women. Hypertension, 45(1): 86-91.

[8] Rebrova O.Iu. 2006. Statistical analysis of medical data. The use of STATISTICA application package. Moscow.

[9] Reshetnikov E.A., Akulova L.Iu., Dobrodomova I.S., Elykova A.V., Iakunchenko T.I., Churnosov M.I., 2009. Polymorphism of candidate genes and echocardiographic parameters in pregnant women in normal state and with gestational toxicosis. Bulletin of Peoples' Friendship University. "Medicine" Series, 4: 223-224.

[10] Reshetnikov E.A., Akulova L.Iu., Dobrodomova I.S., Pakhomov S.P., Sorokina I.N., Poliakova I.S., Batlutskaia I.V., Churnosov M.I., 2011. A study of the role of body mass index in the nature of the association of genetic polymorphisms of vasoactive hormones with blood pressure in women at the end of pregnancy. Scientific statements of BSU. "Medicine. Pharmacy" Series, 4 (99): 153-159.

[11] Reshetnikov, E.A., Akulova, L.Y., Dobrodomova, I.S., Dvornyk, V.Y., Polonikov, A.V., Churnosov, M.I., 2015. The insertion-deletion polymorphism of the ACE gene is associated with increased blood pressure in women at the end of pregnancy. J Renin Angiotensin Aldosterone Syst, 16(3): 623-632.

[12] Roberts, C.B., Rom, L., Moodley, J., Pegoraro, R.J., 2004. Hypertension-related gene polymorphisms in pre-eclampsia, eclampsia and gestational hypertension in Black South African women. Hypertension, 22(5): 945-948.

[13] Sidorova I.S., 2006. Etiopathogenic bases for the management of pregnant women with placental insufficiency. Gynecology, 8 (5-6): 28-32.

[14] Siliberto K.F., Marks G.F., Einstein A., 2006. Pregnancy-associated physiological changes. Surgeon, 12: 25-28.

[15] Sokolnikova I.V., 2008. Parameters of intracardiac and central hemodynamics in the first, second, and third trimesters of normal pregnancy. Siberian Medical Journal, 5: 19-21.

[16] Strutynskii A.V., Roitberg E., 2003. Internal diseases. Cardiovascular system. Moscow.

[17] Zafarmand, M.H., Nijdam, M.E., Franx, A., 2008. The angiotensinogen gene M235T polymorphism and development of preeclampsia/eclampsia: a meta-analysis and meta-regression of observational studies. J Hypertens, 26(9): 1726-1734.

[18] Zatikyan E.P., 2004. Congenital and acquired heart defects in pregnant women. Functional and ultrasound diagnostics. Moscow.