DIAGNOSTIC AND TREATMENT METHODS

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TREATMENT OF CHRONIC ARTERIAL HEPARTENSION DURING PREGNANCY: THE INFLUENCE OF THE STATE OF TARGET ORGANS

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The study presents the results of a comparative analysis of the effect of the hypotensive therapy start time on the condition of target organs (left ventricular (LV) myocardium, kidneys) in 134 pregnant women with chronic arterial hypertension (CAH) and 242 with the development of preeclampsia (PE) on its background. Early hypotensive therapy makes it possible to realize a protective effect on the target organs of pregnant women with CAH (adaptive remodeling of the LV myocardium, renal endothelium (MAU) and purine metabolism (synthesis of uric acid).

Delayed hypotensive therapy (after 15-20 weeks of pregnancy) contributes to the dominance of maladaptive mechanisms of regulating the activity of the cardiovascular system.

These pregnant women are distinguished by the progression of morphofunctional changes in the LV myocardium (concentric hypertrophy and diastolic dysfunction), to the greatest extent with the development of PE. The highest frequency of violations in the circadian rhythm of blood pressure ("non-dipper" and "night-picker" types) and metabolic changes (hyperuricemia, MAU) was found in pregnant women with the development of PE.

Keywords: chronic arterial hypertension (CAH), preeclampsia (PE), diastolic dysfunction (DD), left ventricular concentric hypertrophy, microalbuminuria (MAU), hyperuricemia.

Introduction. The management of pregnant women with hypertensive disorders is complicated: the prescription of drugs is often delayed; the low effectiveness of treatment determines the need for their change and selection of a combination [10,19].

The refusal of patients from hypotensive therapy is associated with the fear of side effects and complications, the risk of unwanted effects on the fetus and the newborn due to penetration through the placenta [2,3].

Current recommendations for the treatment of hypertension in pregnant women include preparations of α-adrenergic agonists (methyldopa), calcium channel blockers (nifedipine), β-adrenergic blockers (labetalol) [4,7,10,18].

Difficulty in achieving the recommended target BP values below 160/110 mm Hg is associated with the risk of violations of the uterine-fetal-placental blood flow and fetal growth retardation during aggressive hypotensive therapy [1,4,7,10,18].

The controversial aspects of the problem of hypertensive disorders treatment during pregnancy are the start time of the therapy and monitoring of its effectiveness. Lack of doctors' awareness about the criteria for early diagnosis can lead to late initiation of treatment and inadequate control of the condition [2].

The prognosis of the course of hypertension during pregnancy, the choice of optimal therapeutic and obstetric tactics implies an assessment of both the degree of the disease (moderate and severe) and the condition of the target organs (features of the structure and function of the left ventricular (LV) myocardium and kidneys).

LV myocardial remodeling in pregnant women with CAH is associated with changes in the size and structure of the organ at the molecular-cellular level on the background of increased hemodynamic load [8]. Morphological correlates of LV remodeling in pregnant women with CAH are considered reactive or progressive with the risk of myocardial hypertrophy. There are practically no studies of the variability of LV myocardial phenotypes in pregnant women with CAH, depending on therapy.

Microalbuminuria (MAU) is believed to be a marker of renal endothelial dysfunction and deterioration of renal function in CAH [2,6,22]. The probability of developing PE and pregnancy complications with MAU in women with CAH is believed to be increased, along with reports of high sensitivity and low positive significance in predicting PE (88.9% and 22.2%, respectively) [13].

The role of hyperuricemia as a marker of gestational complications and PE is actively discussed, especially with an increase in uric acid (UA) from the first trimester of pregnancy [17]. The association of an increased UA level with PE is thought to be stronger on the background of gestational hypertension [9].

An increase in uric acid is proposed to be considered as a cofactor of inflammation of the trophoblast and placenta, contributing to fetal growth retardation (FGR) [22] and premature birth in PE [12].

The objective of the study: to assess the effect of hypotensive therapy start time on the condition of target organs (left ventricular (LV) myocardium, kidneys) in pregnant women with chronic arterial hypertension (CAH) and the development of preeclampsia (PE) on its background.

Materials and research methods. The study contingent consisted of 376 pregnant women: 134 with CAH and 242 with the development of PE on its background. Depending on the timing of the prescription/ start of taking antihypertensive drugs, groups with early and delayed therapy (after 15–20 weeks) were identified: with CAH – n = 58 and n = 76, respectively, the development of PE – n = 114 and n = 128, respectively.

Inclusion criteria: single-child progressing pregnancy, the presence of CAH confirmed before pregnancy, the

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woman's informed consent for the use of biological material for scientific purposes.

The diagnosis of CAH was made on the basis of existing national and foreign recommendations with an increase in SBP ≥140 mm Hg and / or DBP ≥90 mm Hg.

Research methods: office BP measurement, 24-hour monitoring (ABPM) with a Shiller device on an outpatient basis at 10-11th, 21-22nd and 32-33rd weeks of pregnancy in a standard mode at intervals of 15 minutes during daytime hours, at night - 30 min. The following blood pressure indicators were taken into account: systolic, diastolic, pulse, mean arterial pressure (MAP).

Based on the degree of a nighttime decrease in blood pressure or the daily index (DI), the type of the daily curve was determined: "dipper" – patients with DI = 10-20%, characterizing a normal decrease in blood pressure at night, "non-dipper" – with insufficient (DI less than 10%) , "over-dipper" – with an excessive drop in pressure at night (DI more than 20%), "night-picker" – with a negative DI value due to the excess of blood pressure at night compared to the daytime.

The uric acid content in the blood serum was assessed at 6-8 and 16-17 weeks of pregnancy (the norm was 120-450 μmol / l), microalbuminuria (MAU) was determined in the general analysis of urine.

Echocardiography (EchoCG) assessed the main parameters of the LV myocardium and the types of its geometry. For grading, the relative thickness of the LV myocardium was calculated using the formula:

RWT = IVST + LVPWT / EDD, where RWT is the relative thickness of the LV walls, IVST is the thickness of the interventricular septum, LVPWT is the thickness of the LV posterior wall, EDD is the end-diastolic dimension. Criteria for determining the type of LV geometry: normal – LV myocardial mass index (LVMMI) within normal limits, RWT <0.45, concentric remodeling – LVMI within normal limits, RWM> 0.45; concentric hypertrophy – more than normal LVMMI, RWT> 0.45, eccentric hypertrophy – more than normal LVMMI, RWT <0.45. Criteria for LV hypertrophy: LVMMI> 110 g / m2.

LV diastolic function (DF) was analyzed by tissue myocardial Doppler imaging (TMDEchoCG).

Statistical processing of the material was carried out using the IBM SPSS Statistics 19 package. The sample was checked for compliance with the normal distribution using the Shapiro-Wilk test. Methods of parametric and nonparametric statistics were used. The analysis of intergroup differences in terms of qualitative characteristics was carried out using the χ2 test, less than five – the exact two-sided Fisher test. The significance level (p) when testing statistical hypotheses was taken to be p≤0.05.

Results and discussion. The study of the results of 24-hour blood pressure monitoring showed the predominance of the "dipper" type in early treatment of hypertensive disorders in pregnant women (rather than in delayed): almost one and a half times more often in CAH, twice – with the development of PE (p=0.00) (Table 1).

"Abnormal" daily blood pressure profile was detected more often in the absence of early therapy for hypertension: in half of pregnant women with CAH and in the majority with the development of PE. The incidence of "non-dippers", "over-dippers", "night-pickers" in early hypotensive therapy and prevention of placental insufficiency (PI) was significantly lower in the group with the development of PE – one and a half times (p=0.00).

In pregnant women with CAH, the early prescription of antihypertensive drugs determined a slightly higher indicator of the "dipper" type of the diurnal curve; however, there were no intergroup differences with delayed therapy.

The effect of delayed hypotensive therapy was realized in violations of blood pressure circadian rhythms (with a predominance of "non-dipper" and "night-peaker" types), determined by high average daytime, nighttime and daily SBP and DBP indicators in pregnant women with PE on the CAH background. The probability of PE with a mean DBP of 75 mm Hg or more and a mean BP of 90 mm Hg or more at 13-20 weeks of pregnancy is confirmed by other researchers [14].

The effectiveness of early hypotensive therapy proves the prevalence of "dipper" types in pregnant women with CAH and the development of PE, indicating a decrease in average daily blood pressure.

Early drug therapy for hypertensive disorders reduced the frequency of impaired LV relaxation function in comparison with the delayed one (20.9% vs 35.6%) (p=0.01) (Figure 2).

Delayed hypotensive therapy influenced the greater frequency of LV DF disorders in pregnant women with the development of PE – one and a half times (p=0.01). The tendency for the predominance of normal relaxation function of the LV occurred in the early treatment of hypertensive disorders in pregnant women (79.1% vs 64.4%).

Early prescription of antihypertensive drugs reduced the violations of LV relaxation in diastole in CAH by half (p=0.004), in the development of PE – by three times (p=0.00) (Figure 3).

Early therapy determined a lower frequency of diastolic dysfunction (DD) in the sample of all pregnant women with hypertensive disorders – 22.6%, three times less often than with the preserved ability of the LV myocardium to relax (78.2%).

The triggering factors for the development of diastolic dysfunction (DD) are considered to be a combination of hormonal, neurohumoral and metabolic processes underlying maladaptive remodeling of the myocardium with subsequent cardiomyocyte hypertrophy [8]. An early intake of antihypertensive drugs

Daily blood pressure profile of pregnant women, depending on the start of hypotensive therapy

Groups			N	2 trimester		3 trimester	
				dipper	other variants	dipper	other variants
Chronic arterial hypertension (CAH)	Early therapy	абс.	58	38	20	36	22
		%		65.5	34.5	62.1	37.9
	Delayed therapy	абс.	76	37	39	41	35
		%		48.7	51.3	53.9	46.1
Preeclampsia on the chronic arterial hypertension (CAH) background	Early therapy	абс.	114	68	46	52	63
		%		59.6	40.4	45.6	55.3
	Delayed therapy	абс.	128	34	94	50	83
				26.6	73.4	39.1	64.8
				p_{2-4}=0.002 p_{3-4}=0.00	p_{2-4}=0.002 p_{3-4}=0.00		p_{2-4}=0.01

improves the conditions for LV relaxation by reducing the processes of hypertrophy and structural disorganization of cardiomyocytes. Delayed prescription of antihypertensive drugs in CAH was accompanied by an increase in LV stiffness and a decrease in its ability to relax. An increase in diastolic stiffness and a change in the trophic skeleton under conditions of metabolic disorders formed the basis of DD in pregnant women with the development of PE with untimely hypotensive therapy.

The results of the analysis of the correlation between the types of LV geometry and MAU in pregnant women with hypertensive disorders at different periods of hypotensive therapy initiation are presented in Figure 4.

The largest number of pregnant women with MAU was determined in the group with delayed hypotensive therapy, with concentric LV hypertrophy – almost five times more often than remodeling (p=0.00). Early hypotensive therapy contributed to the reduction in MAU MAU in pregnant women, more often detected in concentric LV hypertrophy.

The highest frequency of MAU was found in the group of pregnant women with concentric LV hypertrophy – almost three times with delayed hypotensive therapy in comparison with early therapy (p =0.0005) (Figure 5).

Pregnant women with normal LV geometry and concentric remodeling were distinguished by lower MAU frequency during early hypotensive therapy, however, no statistically significant differences were found in comparison with delayed hypotensive therapy.

The effectiveness of early hypotensive therapy was manifested by the predominance of LV remodeling adaptive mechanisms and a low frequency of MAU in pregnant women with CAH. Delayed prescription of antihypertensive drugs led to pronounced structural and functional disorders of target organs – LV concentric hypertrophy and damage to the renal epithelium.

Hyperuricemia (HU) in the sample of pregnant women with hypertensive disorders was noted more often with delayed hypotensive therapy: in the second trimester – in a third of all patients with CAH, one and a half times more often –with the development of PE (p=0.00) (Figure 6).

In the sample with early hypotensive therapy, an increased uric acid (UA) content was determined in a small number of all pregnant women with CAH (6.9% on average), 42.1% of patients with the development of PE in the second trimester,

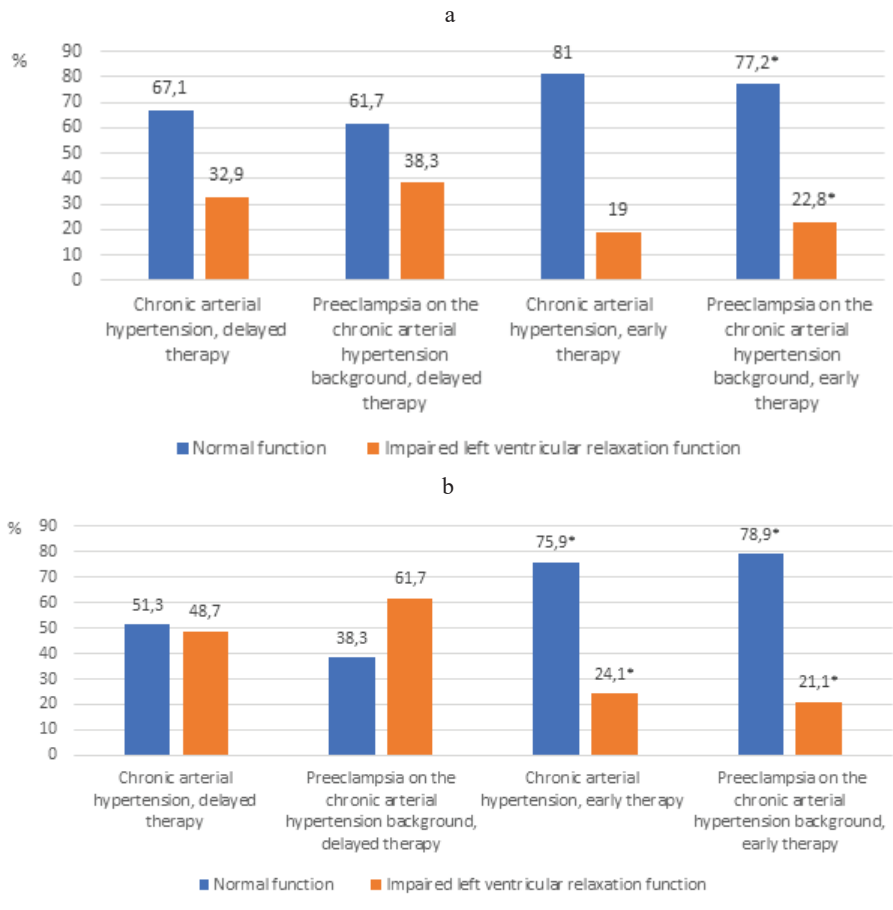

Fig. 1. Features of LV diastolic function (a - in the second, b - in the third trimester) depending on the timing of CAH therapy: (p <0.05) - statistically significant differences from the same groups without treatment in pregnant women * with CAH, ** s PE on the background of CAH

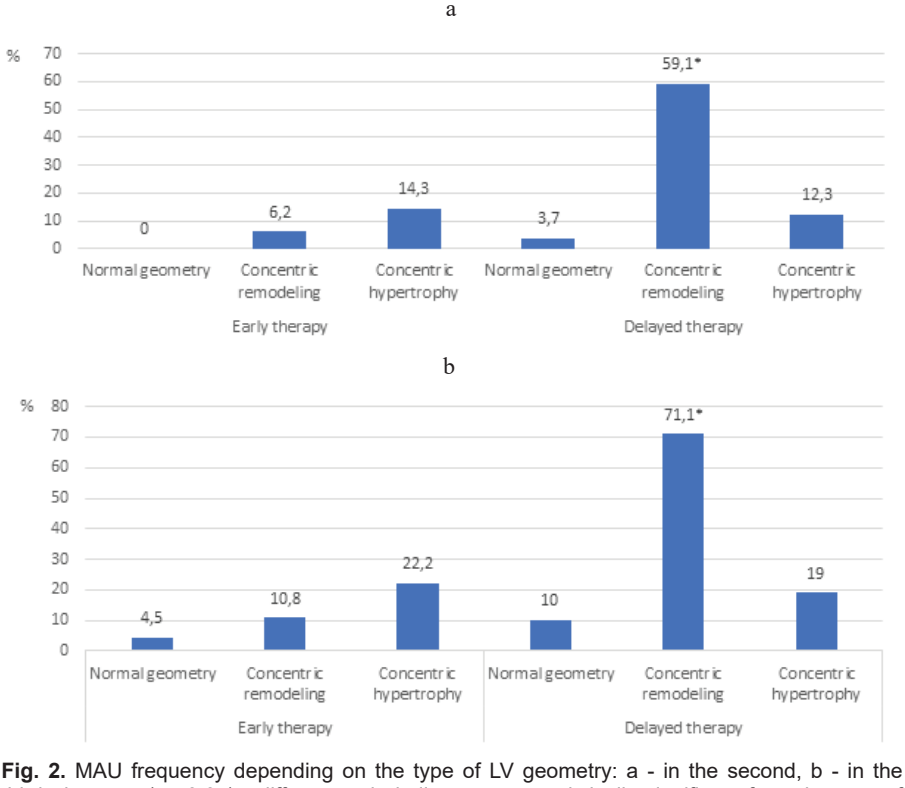

Fig. 2. MAU frequency depending on the type of LV geometry: a - in the second, b - in the third trimester. (p <0.05) - differences in indicators are statistically significant from the type of geometry: * concentric left ventricular hypertrophy in the early therapy group

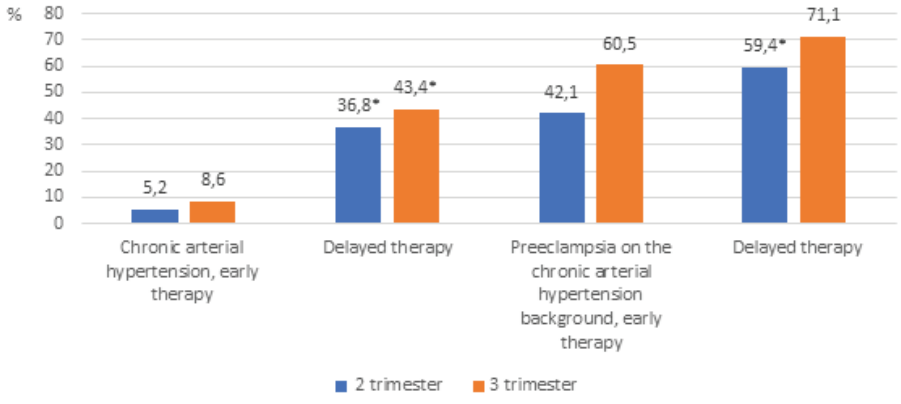

Fig. 3. Frequency of hyperuricemia (HU) depending on the start of hypotensive therapy in the second and third trimesters. (p <0.05) – differences in indicators are statistically significant depending from groups of the same name with early hypotensive therapy in pregnant women with CAH, ** - with PE on the CAH background

60.5% – in the third one. The increased content of MC in pregnant women with the development of PE with delayed therapy was significantly more often detected than with early detection in the second trimester (p=0.009).

The data we have obtained allow us to challenge the opinion about the inexpediency of routine testing for hyperuricemia (HU) [20]. The prognostic significance of increased uric acid (UA) values was established as a predictor of PE, preceding morphofunctional restructuring of the LV myocardium in pregnant women with CAH. Our results do not contradict the data [11] that the level of UA ≥357 μmol/l is associated with proteinuria and increased DBP.

An increase in hyperuricemia in pregnant women with CAH simultaneously with MAU was consistent with the data on a decrease in renal excretion on the background of parenchymal damage [5,21].

The data obtained by us during a comprehensive examination of pregnant women with CAH allow us to note changes in the LV myocardium and impaired diastolic function (DF) as markers of disadaptive cardiac remodeling [15,16], the most significant in the absence of early hypotensive therapy.

Conclusion. Our data confirm the important role of delayed hypotensive therapy in the formation of maladaptive LV remodeling with a predominance of concentric LVH, violations in circadian BP rhythms (prevalence of "non-dippers" and "night pickers") and metabolic disorders (hyperuricemia, MAU). The protective effect of early therapy with antihypertensive drugs in pregnant women with CAH determines the adaptive nature of cardiac remodeling and metabolic changes caused by endothelial renal dysfunction (MAU) and moderate disturbance of purine metabolism (uric acid).

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