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## Ways of endothelial dysfunction correction in pregnant women with arterial hypertension

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### Abstract

Arterial hypertension can significantly impair the health of pregnant woman and often causes early development and progression of gestational and perinatal complications. Endothelial dysfunction is considered to be one of the pathogenetic mechanisms of the development of this pathological condition. The aim of the study was to evaluate the effect of different antihypertensive therapy programs in pregnant women with chronic arterial hypertension.

**Materials and methods:** 64 pregnant women with chronic arterial hypertension on 30-36 weeks of gestation were examined. For the clinical assessment of the pregnant women state there were considered: monitoring of the blood pressure, echocardiography, blood and urine analyses, proteinuria assessment. To evaluate the function of the endothelium, the modified D. Celermajer technique was used; to evaluate the functional state of the fetus cardiotocography (CTG) and the fetal biophysical profile (BPP) were used. Endothelin -1 concentration and the number of desquamated endotheliocytes in the blood serum were studied for the evaluation of biochemical markers of endothelial function.

**Results of the study and their discussion:** It was found that, in pregnant women with arterial hypertension during the initial stage there is a central and peripheral hemodynamics disorder, and its severity directly correlates with the severity of the endothelial dysfunction and an increased risk of gestational and perinatal complications.

**Conclusions:** Tight control of arterial hypertension with normalization of arterial pressure due to inclusion of nebivolol hydrochloride (highly selective beta-blocker with vasodilating properties) in the management program allows to prevent the progression of endothelial dysfunction and aggravation of hemocirculation disorders, including the mother-placenta-fetus system. This fact ultimately leads to normalization of Manning score (parameters of biophysical profile).

**Keywords:** Pregnancy, arterial hypertension, endothelin-1, desquamated endothelial cells, endothelium-dependent vasodilation, endothelial dysfunction, nebivolol hydrochloride

### Introduction

Pregnancy and delivery on the background of arterial hypertension can significantly aggravate the worsening of pregnant woman condition, and often leads to the early development and accelerated progression of gestational complications [1]. One of the major mechanisms of the arterial hypertension (AH) and its complications development is a vascular endothelium dysfunction, that was confirmed by experimental and clinical trials [1, 2, 3]. In healthy people, the functioning of the endothelium promotes regulation of hemodynamic homeostasis and, in physiological conditions, ensures constancy and ductility of arterial pressure (AP) [5, 6]. The endothelium of the vessels supports vascular homeostasis, performing a number of important functions: modulation of vascular tone, regulation of transport of dissolved substances through the vascular wall, inflammatory and reparative processes in response to local injury, and others. [4, 9].

However, today it has been established that the basic mechanisms of endothelial dysfunction progression is the alteration of endothelial nitric oxide (NO) synthesis and release. NO is one of the most important vasodilatation regulators. The leading cause of NO deficiency in hypertension is the NO destruction or NO capture with free radicals that launches the mechanism of endothelial dysfunction, which is an important prerequisite for the development of hypertension [3, 4, 8]. Thus, in general, an erroneous circle is formed that can increase the pathological changes for the pregnant woman and provoke the development of complications for both mother and fetus [1, 6, 7].

However, in recent years and until now, there are controversies between conceptions of tight and less tight control of arterial pressure in pregnant women with arterial hypertension.

The impact of different arterial hypertension management programmes in pregnant women have been discussed in recent years. Tight and less tight control of AH at pregnancy are debated up to now about the percentage of superimposed preeclampsia, the number of obstetric bleeding, the number of fetal distress cases or severe forms of IUGR, perinatal mortality and stillbirth, pulmonary artery thrombosis and intracerebral hemorrhage or other complications in the mother's disability. [1, 2, 3, 7].

Exactly these assumptions become a rationale for the study of the functional state of vascular endothelium in pregnant women with arterial hypertension and its dynamics under the influence of various programs of antihypertensive therapy.

**The purpose of the trial:** Evaluation of the effects of various programs of antihypertensive therapy in pregnant women with chronic hypertension by studying the clinical status of the mother and the fetus, monitoring blood pressure and hemodynamic parameters of the pregnant woman and their correlation with the serum levels of endothelin-1 and the number of desquamated endothelial cells.

**Materials and methods of research:** 64 pregnant women with chronic arterial hypertension stage 2, were examined in the extragenital pathology department of the Ternopil Regional Mother and Child Perinatal Center (2015-2017). All standard clinical analyses and investigations were provided: clinical blood and urine tests, biochemical blood tests, assessment of proteinuria, ECG, echocardiography, ultrasound of the kidneys and peripheral vessels (approved by the Ministry of Health Ukraine (Protocol № 676 and № 384 "Management of hypertensive disorders while pregnancy)).

The trial included 30-36 weeks of gestation pregnant women. For the clinical assessment of the pregnant women, the following factors were taken into account: an increase in blood pressure of more than 160 mm Hg of systolic and 100 mm Hg diastolic; presence of left ventricular hypertrophy on electrocardiogram, echocardiography, intima-media thickening of carotid arteries  $\geq 0,9$  mm generalized narrowing of the retinal arteries; transient microalbuminuria and/or creatininemia the upper limit of normal or increase in plasma creatinine concentration of more than 107-124 mg / dL.

To evaluate the function of the endothelium and its effect on hemodynamics in the mother-placenta-fetus system, the modified method according to D. Celermajer technique was applied [5]. The endothelium-dependent vasodilatation (EDVD) of the brachial artery (BA) was measured on the ultra-sound equipment Aplio-MX Toshiba Medical System, Japan. Initially, the diameter of the brachial artery (the distance between the opposite walls of the artery) was measured in the systolic phase using a 7 MHz transducer placed 5-6 cm higher than the elbow bend, then using a 2.5 MHz pulse-wave Doppler transducer in Doppler mode was used for measuring the change of the blood flow velocity. The stimulus of EDVD was reactive hyperemia, which was provided by the pumping pressure into the cuff, which was applied to the site more distal to the site of the study. After auscultation, the blood pressure was measured. In the cuff pressure was pumped for 5 minutes up to 50 mm Hg higher than systolic. After 5 minutes the cuff was taken away. Measurement of the diameter of the artery was performed for

the first minute and again after 5 minutes. An increase of the diameter of the brachial artery after 60-90 seconds over 10% was considered to be a normal reaction. A lower degree of dilation or vasoconstriction was evaluated as a pathological reaction.

To assess the functional state of the fetus, cardiotocography (CTG) was used with a rating on the Fisher's scale and biophysical profile of the fetus (BPP) as the most comprehensive scale for fetal well-being evaluation (the BPP scale was used according to Order No. 900 of December 27, 2006, which took into account 5 parameters: fetal heart rate, fetal breathing, fetal movements, fetal tone, amniotic fluid volume).

The study of biochemical markers of endothelial function was carried out by assessment of the concentration of endothelin-1 and the number of desquamated endothelial cells in blood serum. The immunoenzymometric assay was used for determination of endothelin-1 in blood serum using Biomedica reagents «Medizinprodukte GmbH and Co KG» (Austria). The number of desquamated endothelial cells in the blood serum was determined by Hladovec J. method in the modification of Petrishchev NN *et al.* [9, 10].

Pregnant women of the Group I (22 women) started the basic antihypertensive therapy that included methyldopa 250 mg 4 times a day from 23 weeks of gestation. Group II patients (21 pregnant women) after 30 weeks of gestation were additionally assigned nebivolol hydrochloride (highly selective  $\beta_1$ -receptor blocker with nitric oxide-potentiating vasodilatory effect) for 5 mg per day. The control group included 21 pregnant women (apparently healthy with singleton pregnancies and without somatic pathology, matched by age and gestation term with patients of group I and II).

Biochemical studies, CTG and biophysical profile assessment were carried out in 30 weeks of pregnancy. Clinical results of treatment were evaluated after 4 weeks. However, women of the second group because of clinical efficacy continued treatment up to childbirth.

Statistical processing of the obtained data was performed in the department of systemic statistical research of the State Higher Educational Establishment "I. Ya. Horbachevsky Ternopil State Medical University of Public Health Ministry of Ukraine" in the software package Statistica (Windows, v. 10).

**The results and their discussion:** Average blood pressure values in pregnant women of Groups I and II exceeded the norm and amounted to 156.2 - 156.8 mm Hg, respectively - systolic and 108.8-106.4 mm Hg - diastolic (Table 1). These women were confirmed with arterial hypertension II st. and signs of hyperdynamic syndrome, which posed a threat to the physiologic progress of pregnancy. Thus, the average biophysical profile of the fetus in this groups was only  $7.00 \pm 0.12$  points compared to  $9.21 \pm 0.15$  points in the control; At the same time, a stably low assessment of the rhythm of the fetal heart rate on CTG was noted (Fisher's scale assessment  $7.55-7.68 \pm 0.13$  points against  $8.88 \pm 0.16$  points,  $p < 0.05$ ). Simultaneously, an increase in heart rate to  $89 \pm 3$  beats / min and a significant decrease in endothelial function of peripheral vessels were noted in these pregnant women (EDVD =  $8.8 \pm 1.4\%$  versus  $18.13 \pm 1.4\%$  in the control  $p < 0.05$ ).

**Table 1:** Changes of hemodynamics indexes and functional state of the fetus under the influence of the proposed treatment programs (M ± (m))

Experimental groups		SBP, mm Hg	DBP, mm Hg	Heart rate, beats/ min	Endothelium dependent vasodilatation (EDVD), %.	Restoration of blood flow velocity, %	The average score of CTG scores (scale Fisher)	The average biophysical profile estimation
I group, n = 22	1	156.2 ± 2.6	108.8 ± 3.2	86 ± 3.0	8.0 ± 1.4	38.4	7.68 ± 0.9	7.00 ± 0.7
	2	146.4 ± 2.2 *	98.6 ± 2.4 *	88 ± 5.0 *	12.4 ± 1.6 *	41.8	8.02 ± 0.7	7.27 ± 0.6
II Group, n = 21	1	156.8 ± 3.6	106.4 ± 3.2	86 ± 3.0 *	8.3 ± 1.4	38.4	7.55 ± 0.3	7.00 ± 0.7
	2	132.6 ± 2.6 *	90.2 ± 2.2 *	68 ± 4.0 *	16, 2 ± 1.2	64.6	8.56 ± 0.6	7.86 ± 0.2
III group (control), n = 21		118.4 ± 2.4 *	78.8 ± 3.2	78 ± 3.0	18.3 ± 1.4	74.2	8.88 ± 0.6	9.21 ± 0.5

Note. 1, 2 - indicators before and after treatment

The underlined values of the indexes differ significantly from the data control;

\* - The difference is reliable compared to the pre-treatment data (R <0.05).

The use of conventional antihypertensive therapy led to normalization of blood pressure in 9 (41%) of pregnant women of the first group, and in 6 (27%) to a significant decrease in blood pressure without its normalization. This treatment was not accompanied by restoration of endothelial function of blood vessels and heart rate, nor did it lead to an improvement in the biophysical profile of the fetus.

In pregnant women in the second group, additional use of nebivolol hydrochloride for 3-4 days led to normalization of systolic and diastolic blood pressure in 18 (86.0%), as well as a significant reduction in blood pressure in the rest of the patients. In these pregnant women, under the influence of treatment with nebivolol hydrochloride, a moderate decrease in heart rate (up to 68 ± 4.0 beats / min) and restoration of endothelial function of peripheral vessels was observed (EDVD under the influence of treatment increased from 8.3 ± 1.4% to 16, 2 ± 1.2%). Restoration of hemodynamic in pregnant women in this group was accompanied by a positive effect on BPP, which reached 8.86 ± 0.12 points (in the control 9.21 ± 0.15, p<0.05).

At the same time, it should be noted that according to our research, the baseline EDVD in women of Group I was 8.0 ±

1.4% and increased only to 12.4 ± 1.6% after treatment. In pregnant women whose treatment program included nebivolol hydrochloride, which had an endothelial-modulating property, EDVD after treatment increased to 16.2 ± 1.2% and did not differ significantly from the level of EHD in healthy pregnant women (18.3 ± 1.4%).

Thus, the obtained results indicate that the proposed therapy caused the normalization of central and peripheral hemodynamics, positively influenced the functional state of the endothelium of blood vessels, which ultimately resulted in the normalization of the fetal state.

It is also important, in our opinion, to assess the effect of treatment on the morpho-functional state of the endothelium, since its structural changes and functional decompensation can lead to the development of preeclampsia (over imposed gestosis) or the malignant progression of hypertension, with the formation of complications for the mother or the development of distress of the fetus [1, 3, 6, 7].

To answer this question, we studied the dynamics of the number of circulating desquamated endothelial cells and endothelin-1 in serum of the investigated groups (Table 2).

**Table 2:** Dynamics of endothelium functional state indicators in blood serum under the influence of various programs of antihypertensive therapy in pregnant women with arterial hypertension.

Parameters	Before treatment	After treatment		Healthy pregnant women
	I and II group, n = 43	I group, n = 22	II group, n = 21	III group, n = 21
Endothelin-1, pmol/ l	0.287 ± 0.025 p<0.01	0.112 ± 0.034 p<0.05	0.069 ± 0.008 p<0.01	0.046 ± 0.014
Number of circulating desquamated endothelial cells, 10 <sup>4</sup> / L	13.95 ± 2.75 p< 0.05	10.08 ± 1.33 p<0.05	7.34 ± 1.65 p<0.05	5.85 ± 1.22

**Note:** reliability - the difference of values comparing to the control group; p<0.05 - data accuracy.

Physiological pregnancy is characterized by the balance of the basic vasoactive factors of endothelial origin, namely, the low level of endothelin-1 in plasma, and the adequate response of the brachial artery to occlusion. In pregnant women with arterial hypertension, EDVD disorder is associated with an increased content of endothelin-1 in the blood plasma and an increase of the desquamated endothelial cells number.

The role of endothelin-1 as a recognized marker of endothelial dysfunction is documented in many studies [3, 4, 6]. Endothelin-1 is a biologically active peptide, which is one of the most powerful vasoconstrictor mediators. In the implementation of the vasoconstrictive effect of endothelin in

perinatal pathology is the direct damage to the endothelium and increased sensitivity of the vascular wall to norepinephrine and serotonin [3, 9]. There are data on the effect of endothelin-1 on coronary and cerebral vessels and central regulation of blood pressure. It is also established that endothelins play an important role in the regulation of uterine and placental arteries tonicity, showing the constrictor influence on the placental and umbilical cord vessels [3, 4, 6].

When examining the serum level of endothelin-1 in pregnant women of the 1 and 2 groups, it was established that its initial level (before treatment) was significantly higher comparing to the control group of healthy pregnant women (Table 2). Thus,

the concentration of endothelin-1 was  $0.287 \pm 0.025$  pmol /l, and the number of desquamated endothelial cells was  $13.95 \pm 2.75 \times 10^4$ /l. Simultaneously the same indices in healthy pregnant women were  $0.046 \pm 0.014$  pmol / l and  $5.85 \pm 1.22 \times 10^4$ /l, respectively.

The proposed treatment program proved its clinical effectiveness (lowering blood pressure and improving the BPP and Fisher scale) and decreased in direct correlation to the level of endothelin-1 and number of desquamated endothelial cells. So, the patients with AH at monotherapy with methyldopa had clinically moderate efficiency and insignificant decrease of endothelin-1 serum level in Group 1. The median in this group was  $0.112 \pm 0.034$ , and the level of desquamated endothelial cells decreased insignificantly (from  $13.95 \pm 2.75 \times 10^4$ /l to  $10.08 \pm 1.33 \times 10^4$ /l). In 2 patients from this group, the clinical effect could not be achieved, they had a combined gestosis, the same patients had a paradoxical reaction of EDVD. Instead of expanding the brachial artery in the first 90 seconds contracted (11%), with further vasodilation, but without restoration of the blood flow velocity in the brachial artery. Simultaneously these same patients observed further growth of endothelin-1 serum level and increasing desquamated endothelial cells number.

In 22 patients of group II there were no cases of combined gestosis development. Better control of blood pressure (SBP =  $132.6 \pm 2.6$  and DBP =  $90.2 \pm 2.2$  mm Hg) was achieved and the values of the Fischer's scale and BPP were significantly higher. The levels of endothelin-1 (from  $0.287 \pm 0.025$  pmol / l to  $0.069 \pm 0.008$  pmol / l) and the number of withdrawn endothelial cells (from  $13.95 \pm 2.75 \times 10^4$  / l to  $7.34 \pm 1.65 \times 10^4$  / l) decreased. The results of the morpho-functional status of the endothelium in the pregnant women of the group 2 after treatment were approximate to the indicators of the group of healthy pregnant women. Thus, the level of endothelin-1 after treatment in pregnant women in Group II was  $0.069 \pm 0.008$  pmol / l comparing to  $0.046 \pm 0.014$  pmol / l in healthy pregnant women, and the number of desquamated endothelial cells was  $7.34 \pm 1.65 \times 10^4$ /l comparing to  $5.85 \pm 1.22 \times 10^4$ /l in healthy pregnant women. The data obtained by us confirm the concept of the pathogenetic role of endothelial dysfunction in the development of hypertension in pregnant women.

It has been established that high blood pressure in pregnant women is accompanied by endothelium dysfunction, which negatively affects the condition of the fetus, as evidenced by the significantly lower parameters of the CTG (Fisher's scale) and parameters of the biophysical profile.

Comparison and analysis of the results between the experimental groups, specifically, the correlation between number of desquamated endothelial cells, endothelin-1 serum levels, endothelial-dependent vasodilatation, and the score of BPP and CTG (Fisher's scale), leads us to the conclusion that vascular endothelial dysfunction is accompanied by a negative effect on a pregnant woman and is a prognostic disadvantage for gestation. The disturbances of endothelial function in pregnant women with untreated hypertension provoke the development of pregnancy complications and violations of circulation in the mother-placenta-fetus blood flow, which is clinically manifests with decreased fetal activity, a tendency of IUGR (intrauterine growth restriction) or small for gestational age weight, as well as poorer results of BPP and Fisher's scale.

Basic treatment helps to lower blood pressure and improve

the clinical status of pregnant, but in pregnant women of the first group receiving treatment with methyldopa there were significantly higher parameters of systolic and diastolic arterial pressure, heart rates and lower score of the biophysical profile and Fisher's CTG scales. Inclusion in the complex treatment of highly selective betablocker nebivolol hydrochloride (which has vasodilating properties due to modulation of nitric oxide synthesis) for pregnant of the II group, helps to normalize the parameters of central and peripheral hemodynamics in a significantly greater number of patients, prevents the development of hemodynamic disorders in the mother-placenta-fetus system and reduces the frequency of gestational and perinatal complications.

## Conclusions

1. Arterial hypertension in pregnant women requires tight control of blood pressure with its normalization, which prevents the progression of vascular endothelial dysfunction and aggravation of the central and peripheral hemodynamic disorders, including in the mother-placenta-fetus system.
2. It is advisable to use a non-invasive method for assessing the state of the endothelium for the effectiveness of control over the progressing of arterial hypertension, assessment of hemodynamic disorders and the efficacy of treatment of hypertensive disorders in pregnant women. Proposed and tested methods for evaluating the morpho-functional status of the endothelium could be used to predict the appearance of gestational and perinatal complications.
3. The aggravation of endothelial dysfunction in combination with the aggravation of hemodynamic disorders in pregnant women and in the mother-placenta-fetus circulation can predict the malignant course of hypertension in pregnant women, and the significantly higher risk of preeclampsia over imposing and intrauterine fetal growth restriction.
4. The inclusion of a highly selective beta-blocker (nebivolol hydrochloride) with vasodilating properties additionally to the conventional therapy promotes effective control of blood pressure and is accompanied by restoration of vascular endothelial function and normalization of central hemodynamics and blood flow in the mother-placenta-fetus system, which ultimately leads to normalization of the biophysical profile of the fetus.

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