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The role of arterial hypertension in the development of cerebrovascular diseases in pregnancy

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Abstract

Nowadays, the risk factors, improvement of diagnosis and treatment of cardiovascular diseases are of particular interest. Arterial hypertension (HTN) is known to contribute to cardiovascular disease and to be a risk factor for cerebrovascular diseases. HTN during pregnancy and in the postpartum period draws particular attention. Throughout the world, hypertension during pregnancy remains the leading cause of maternal and child morbidity and mortality. To our knowledge, only a few works studied neurological disorders associated with HTN in pregnant women. In this connection, the purpose of our review was to analyze the role of HTN in the development of cerebrovascular diseases in pregnancy. Pregnant women with HTN show 5,2-fold higher frequency of strokes than normotensive women. The risk of stroke increases from the third trimester of pregnancy to six weeks of the postpartum period. The pregnant women with HTN develop changes in the coagulation system leading to the formation of arterial and venous thromboses in the cerebrovascular circulation. The presence of preeclampsia (PE) is associated with the 7–9-fold increase in the risk of stroke. Endothelial dysfunction is one of the leading links in the pathogenesis of PE. The PE is associated with an increase in anti-angiogenic factors and a decrease in angiogenic factors. Thus, the measures preventing the development of cerebrovascular diseases in pregnant women with HTN, include identification of prehypertension in women of childbearing age, the improvement of HTB management strategies, and an interdisciplinary approach to the diagnostic and treatment process involving the obstetrician, the therapist, the cardiologist and the neurologist.

Key words: hypertension, pregnancy, preeclampsia, stroke

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Роль артериальной гипертензии в развитии цереброваскулярных заболеваний при беременности

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Резюме

В настоящее время особое внимание уделяется изучению факторов риска, совершенствованию диагностики и лечения сердечно-сосудистых заболеваний. Установлено, что артериальная гипертензия (АГ) вносит основной вклад в структуру данной патологии. Доказано, что АГ может выступать в роли фактора риска для цереброваскулярных заболеваний. Особое значение АГ имеет во время беременности и в послеродовом периоде, так как во всем мире АГ во время беременности остается ведущей причиной материнской и детской заболеваемости и смертности. В доступной научной литературе имеются лишь единичные работы, посвященные поражениям нервной системы, ассоциированным с АГ, у беременных. В связи с этим целью нашего обзора стал анализ роли АГ в развитии цереброваскулярных заболеваний при беременности. Показано, что при АГ у беременных инсульты возникают в 5,2 раза чаще, чем у беременных с нормальными показателями артериального давления. Риск инсульта увеличивается с третьего триместра беременности до шести недель послеродового периода. У беременных с АГ происходят изменения в системе гемостаза, что приводит к образованию артериальных и венозных тромбозов головного мозга. Наличие преэклампсии (ПЭ) увеличивает риск инсульта в 7–9 раз. Одним из ведущих звеньев патогенеза ПЭ считается эндотелиальная дисфункция. Изучение биологически активных веществ при беременности, осложненной ПЭ, выявило повышение антиангиогенных факторов и снижение ангиогенных факторов. Таким образом, для предупреждения развития цереброваскулярных заболеваний у беременных с АГ требуется выявление предгипертензии у женщин детородного возраста, совершенствование методов лечения АГ, усиление нейропротективных процессов, для чего необходим междисциплинарный подход к диагностическому и лечебному процессу с участием акушера-гинеколога, терапевта, кардиолога и невролога.

Ключевые слова: артериальная гипертензия, беременность, преэклампсия, инсульт

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At present, special attention is paid to the risk factors, improvement of diagnosis and treatment of cardiovascular diseases characterized by widespread, high disability and mortality. It was established that arterial hypertension (AH) makes the main contribution (about 42%) to the structure of this pathology. In our country in 2015, 21.7 million people underwent medical examination. The incidence of AH was 33.6%, including 16.5% for the diagnosis of the disease, 3.6% for the diagnosis as a preliminary diagnosis, and 13.5% for the increase in blood pressure (BP) as a risk factor [1]. It has been shown that AH can act as a risk factor for diseases of the nervous system, such as transient ischemic attacks, acute cerebrovascular disorders, cognitive dysfunction, up to the development of dementia [2]. Particular importance of AH is during pregnancy and in the postpartum period. Throughout the world, AH during pregnancy remains the leading cause of maternal and child morbidity and mortality [3]. It is known that the diagnosis and classification of AH in pregnancy differs in its characteristics. Thus, the criterion of AH in pregnant women is an increase in systolic BP (SBP) > 140 mm Hg and/or diastolic BP (DBP) > 90 mm Hg stages determined by two measurements with an interval of 4 hours [4]. Several forms of AH are distinguished: one existing before pregnancy and one developing during pregnancy. The first group includes chronic AH, the second group includes — gestational hypertension, which developed after the 20th week of pregnancy and disappears before 12 weeks after delivery, preeclampsia (PE). In accessible scientific literature there are only a few works devoted to the nervous system lesions associated with AH in pregnant women. In this connection, the aim of our review was to analyze the role of AH in the development of cerebrovascular diseases in pregnancy.

The determining role of AH in the development of the stroke is convincingly shown in concrete job [5]. In a study that included 81 983 216 hospitalizations during pregnancy between 1994 and 2011, 31 673 (3.8 per 10 000 cases) were required for strokes, of which 9 890 had AH. During this period, there was an increase in strokes on the background of AH during pregnancy from 0.8 to 1.6 per 10 000. Stroke with AH was more common in women aged 25 to 35 years (4,617 cases — 46.7%). It is shown that with AH in pregnant women, stroke appear 5.2 times more often than in pregnant women with normal indices of blood pressure. The presence of PE and eclampsia increases the risk of stroke by 7–9 times [6]. The incidence of stroke during pregnancy varies from 4.2 to 210 per 100 000 pregnancies [7]. Such differences in epidemiological indicators, apparently, are due to the difficulties in conducting differential diagnosis during pregnancy. A full-fledged examination of the patient with suspicion of stroke and the interpretation of the results obtained may be hampered by pregnancy [8].

According to French researchers, stroke occurred in 10 per 100 000 pregnancies [9]. At the same time hemorrhagic strokes prevailed — 74%; on ischemic — accounted for 24%; in 2% of cases there were combinations of hemorrhagic and ischemic strokes. In total, from 2010 to 2012 years, there were 22 cases of maternal deaths associated with the stroke. The authors believe that pregnancy, apparently, increases the risk of rupture of anomalies of cerebral vessels: aneurysms, arterio-venous malformations and cavernous angiomas, especially if there is AH. It is believed that the development of sudden, unusual, intense headache in a pregnant woman requires neuroimaging, including magnetic resonance imaging of the brain, magnetic resonance angiography, computed tomography in vascular mode with contrast to exclude abnormalities of the brain vessels. According to Japanese researchers who studied cases of strokes during pregnancy, hemorrhagic stroke was associated with gestational hypertension in 11.7%. [10]. According to statistics, the risk of stroke increases from the third trimester of pregnancy to 6 weeks of the postpartum period [11]. There is evidence that the frequency of strokes associated with pregnancy may be 30 per 100 000 pregnancies, not only ischemic and hemorrhagic stroke, but also venous cerebral infarction due to thrombosis of cerebral sinuses or veins [12]. In the presence of AH, another cerebrovascular disease in pregnant women and in the postpartum period may be the syndrome of the posterior reversible encephalopathy syndrome (PRES), which is manifested by visual disturbances, headache, convulsive attacks, a disturbance of consciousness, vomiting. PRES develops against the background of high blood pressure, which leads to the development of vasogenic edema mainly in the parieto-occipital region of the brain. Diagnosis is based on the characteristic clinical data and the results of neuroimaging (CT or magnetic resonance imaging of the brain) to confirm vasogenic brain edema and exclude other causes of neurological deficits. With timely adequate therapy, the pathological process has a reverse development, but in the absence of such — leads to irreversible damage to the brain [13, 14].

In pregnant women with AH disorders occur in the system of hemostasis, which, triggering thrombosis of arterial or venous vessels of the brain, contribute to the development of cerebrovascular diseases. It was shown that during pregnancy with chronic hypertension and PE, the number of platelets was reduced, their structure and functional activity were reduced, activated partial thromboplastin time, prothrombin time and prothrombin index were shortened, and the level of fibrinogen was increased [15]. At the same time, pregnancy is accompanied by thrombophilic conditions, which can lead to disruption of adaptation and cause a rise in BP. With the increase in BP, the coagulating potential of blood increases, the DIC-syndrome develops, which increases the risk of thrombotic complications and bleeding [16]. In this relation, during pregnancy, such women need to monitor hemostasis, which includes not only an expanded coagulogram, but also the determination of polymorphisms of genes encoding clotting factors [17].

PE and eclampsia complicate 3–8 % pregnancies, and are the most formidable complications of pregnancy, leading to the development of stroke associated with pregnancy [18]. In the study, which included 91 women with stroke during pregnancy, childbirth and the postpartum period, the incidence of stroke with a background of PE was 18.7% (17 women). More often stroke developed in the III trimester of pregnancy, in childbirth and the postpartum period (64.7%) and in primiparas (70.6%). In 8 out of 17 women with PE, cerebrovascular pathology was detected: arterio-venous malformations, arterial aneurysms, brachiocephalic artery spasm, abnormal AH, hypertonic microangiopathy [19]. The authors concluded that PE and eclampsia increase the risk of development of stroke, which is significantly increased in the presence of pathology of cerebral vessels.

Risk factors for the development of PE are anemia, kidney and urinary tract diseases, varicose veins, hereditary predisposition, chronic hypertension, obesity, extreme obstetric age (younger than 20 years and over 35 years), large interval between births [20]. When evaluating the pathogenesis of AH in pregnant women, evaluation of renal function is particularly important. This is due to the fact that the causes of AH during pregnancy are often: diseases of the kidneys and urinary tract: chronic pyelonephritis; glomerulonephritis; polycystic kidney disease [21]. The detection of renal lesions in AH requires the use of new markers. It is believed that the study of biomarkers such as lipocalin, associated with gelatinase, a molecule of kidney damage, cystatin C, and a hepatic form of a protein that binds to fatty acids may be useful in the early diagnosis of both acute and chronic kidney damage, including hypertensive nephropathy [22].

A study of the predictors of the development of PE in pregnant women with AH revealed the following. The study included 223 pregnant women [23]. Among them were 63 (28.3%) pregnant women with hypertensive syndrome. In 31 (49.2%) pregnant women had chronic AH, 32 (50.8%) had gestational AH. The study did not include women with secondary and unclassified hypertension. Depending on the development of PE, pregnant women with hypertensive syndrome were retrospectively divided into two groups. The first group consisted of 50 pregnant patients with hypertensive syndrome without signs of PE, the second group included 13 women with hypertensive syndrome, who had signs of PE during pregnancy. Dynamics of office BP indicators throughout the pregnancy between the groups did not differ. During daily monitoring of BP at 30 weeks of gestation against a hypertensive syndrome, a more pronounced maximum BP rise in the morning, a daily average pulse BP, a time index of SBP in the morning, a variability of BP at night, a high incidence of AH in the category of "non-dipper" DPB correlated with the risk of developing PE. The presence of diastolic dysfunction of the left ventricle and a decrease in glomerular filtration rate (CKD-EPI) in the third trimester in pregnant women in combination with AH were associated with an increase in the frequency of PE. In the first and third trimesters of pregnancy, the level of cystatin C was higher in the background of the AH ($p = 0.01$, $p = 0.005$, respectively), and the concentration of MMP-2 matrix metalloproteinases (MMP) ($p < 0.001$, $p < 0.001$) and MMP-9 ($p < 0.001$; $p = 0.002$) in the blood was lower in women with PE. The authors believe that an increase in the concentration of cystatin C and a decrease in MMP-2 and MMP-9 levels in early pregnancy in women with AH can be considered as early predictors of the risk of developing PE.

Currently, one of the leading links in the pathogenesis of PE is endothelial dysfunction. It is proved that the functional activity of cerebral vascular endothelial cells is closely related to the state of hemodynamics, BP indicators. Manifestations of endothelial dysfunction, the direction and severity of changes in the formation of individual endothelial factors are due to the heterogeneity of the endothe-

lium and depend on the structure, biochemical organization and organ function. Understanding the differences in the morphology and functions of various subpopulations of endothelial cells is of great importance for the treatment of endothelial dysfunctions, vascular prosthetics, revascularization and regeneration of ischemic organs [24]. Endothelial dysfunction is characterized by changes in microcirculation and increased adhesiveness of the vascular wall, which leads to generalized vascular spasm and circulatory tissue hypoxia. A feature of AH in PE is the involvement of the inflammatory component in the development of endothelial dysfunction and a high level of homocysteine, in contrast to pregnant women with chronic AH [25]. These data indicate the need to study biologically active substances in early pregnancy to identify the predictors of development of PE. Such a study was conducted and included determination of the concentration of vascular (VEGF) and placental (PlGF) growth factors, soluble vasculodothelial growth factor receptor-1 (sVEGF-R1) in pregnancy complicated by PE [26]. The authors examined 105 pregnant women with a gestation period of 32–34 weeks. The main group included 17 (16.2%) women, whose pregnancy was complicated by PE of moderate severity. The control group was 88 (83.8%) pregnant women with uncomplicated pregnancy. The concentration of the PlGF control group was 942.4 ± 241.3 pg/ml, the concentration of the main group was 134.9 ± 73.18 pg/ml ($p < 0.01$). The level of VEGF in the pregnant control group was higher, compared with the level of the vascular growth factor of the main group: 5.3 ± 1.3 and 2.1 ± 0.8 pg/ml, respectively ($p < 0.05$). The concentration of sVEGF-1 in the pregnant control group was 2068.3 ± 323.5 pg/ml, in the main group — 9314.3 ± 1381.0 pg/ml ($p < 0.001$). The prevalence of angiogenic factors over antiangiogenic factors is characteristic for physiological pregnancy. In pregnancy, complicated PE, an increase in antiangiogenic factors and a decrease in angiogenic factors were noted.

Thus, the pathogenetic role of AH in pregnancy in the development of cerebrovascular diseases is beyond doubt. What ways do we have to reduce the risk of development of stroke in pregnant women with AH? On the one hand, prevention and timely treatment of persons with AH are needed, on the other — strengthening of neurotective processes. First of all, it is necessary to improve the therapy of people with AH. The experience of keeping the register of patients with AH, including the expert assessment of medical care for patients with AH based on the allocation of clinical indicators at all stages of the treatment and diagnostic process in accordance with the Russian recommendations for the prevention, diagnosis and treatment of AH gave good results. The use of the computer program with the automated information and analytical system "Register AH" showed a positive dynamics by optimizing the quality control of medical care provided to 1 539 patients with risk factors and AH based on innovative technologies in dynamic outpatient monitoring [27].

One of the most important ways to reduce the frequency of AH among pregnant women should be considered the detection of prehypertension in women of childbearing age. The relevance of this problem is evidenced by the results of a study of the prevalence of prehypertension and its association with risk factors for cardiovascular diseases. Analysis of survey data of 20 607 residents aged 25–65 years in 12 regions of Russia, of which 7 806 men (37.9%) and 12 801 women (62.1%) found that the optimal BP was registered in 3 848 (23.4%) people, normal BP — in 3 551 (20.1%), high normal blood pressure — in 2 861 (14.9%), prehypertension — 6 412 (35.0%), AH — 10 347, which was 41.6% [28]. At the same time, the optimal BP corresponded to the level of BP < 120/80 mm Hg. The normal BP is 120–129/80–84 mm Hg high normal BP of 130–139/85–89 mm Hg AH, the prehypertension of BP is 120–139/80–89 mm Hg AH — BP ≥ 140/90 mm Hg Art or antihypertensive therapy. The probability of developing prehypertension adjusted for sex, age and obesity was associated with an increase in total cholesterol > 4.9 mmol/L (1.27 [1.15, 1.39]), low density lipoproteins > 3.0 mmol/L (1,25 [1.14, 1.37]), triglycerides > 1.7 mmol/l (1.39 [1.23, 1.58]), glucose ≥ 5,6 mmol/l (1,46 [1.28, 1.67], $p < 0.05$). The high prevalence of prehypertension, the association of metabolic shifts with the transformation of optimal BP into prehypertension, which requires its early diagnosis, correction of metabolic risk factors for cardiovascular diseases, is shown.

What are the possibilities of neuroprotection at the present stage? We know that most drugs with neuroprotective effect are not allowed for use in pregnant and lactating mothers. However, new experimental data indicate the possibility of innovative approaches to neuroprotection during pregnancy. When modeling ischemic stroke by occlusion of the middle cerebral artery, the neuroprotective effect of the female reproductive hormone progesterone

and its metabolites is shown [29]. Inactivation of the progesterone receptors in the central nervous system led to a decrease in brain resistance to occlusion of the middle cerebral artery, as evidenced by an increase in the volume of cerebral infarction and an increase in the neurological deficit. It is believed that one can therapeutically influence the progesterone status to achieve neuroprotection in ischemic stroke.

Thus, in order to prevent the development of cerebrovascular diseases in pregnant women with AH, an interdisciplinary approach is required with active participation in the treatment process of the obstetrician-gynecologist, therapist, cardiologist and neurologist.

Conflict of interest
The authors declare no conflict of interest.

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