



Physicians' knowledge and preferences in tactics of management and rational pharmacotherapy of arterial hypertension in pregnant women (PHYGEST study)

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Abstract

Introduction: The issues of rational antihypertensive therapy in pregnant women are always extremely relevant, since high blood pressure in a pregnant woman is associated with serious risks for a mother and a fetus.

The aim of the study: To determine the knowledge and preferences of physicians in the management of pregnant women with arterial hypertension.

Materials and methods: A multicenter study was conducted in 2018–2021 using an anonymous questionnaire among 411 doctors from 8 regions of Russia.

Results and discussion: The levels of knowledge and preferences of specialists in the issues of diagnosing and formulating a diagnosis of arterial hypertension and preeclampsia in pregnant women, prescribing basic and additional drugs for the treatment and prevention of hypertension were revealed, and the degree of compliance with the current clinical guidelines was assessed.

Conclusion: Due to the insufficient level of knowledge of specialists, it is required to pay increased and special attention to this problem, strengthen control over compliance with clinical guidelines, and introduce it into postgraduate recommendations and continuing education programs.

Keywords

arterial hypertension, preeclampsia, pregnant women, antihypertensive therapy, doctors' knowledge level, doctors' preferences, questioning.

Introduction

Arterial hypertension (AH) is a syndrome of increased systolic blood pressure (SBP) ≥ 140 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg. The prevalence of this pathology among the adult population is 30–45% (Kobalava et al. 2020). AH occurs in 10% of pregnant women and is an important contributor to maternal and neonatal morbidity and mortality worldwide. In the Russian Federation, the prevalence of arterial hypertension in pregnant women is 7–30% (Russian Society of Cardiology 2018). According to the Ministry of Health of the Russian Federation, hypertensive complications of pregnancy in the last decade have been ranked the 4th leading cause of maternal death (Russian Society of Obstetrics and Gynecology 2016). About 15–18% of all maternal deaths in the world are associated with the development of hypertension, which is 62.000–77.000 deaths per year (Mravian and Petrukhin 2019). Gestational hypertension is a gender-specific cardiovascular risk factor for women throughout their life (Tsygankova et al. 2014, 2017).

The following clinical variants of hypertension during pregnancy are distinguished:

- Chronic arterial hypertension (CAH) that developed before pregnancy or manifested before the 20th week of gestation and persists for more than 6 weeks after delivery;
- Gestational hypertension (GAH) – a condition induced by pregnancy, which manifests itself for the first time after 20 weeks, with spontaneous normalization of blood pressure within 6 weeks after delivery;
- Preeclampsia (PE) – gestational hypertension with proteinuria >300 mg/day or albumin/creatinine in a single portion of urine >30 mg/gram, in some cases with manifestations of multiple organ failure;
- Preeclampsia that developed against the background of CAH (Chazova and Zhernakova 2019; Kobalava et al. 2020).

In addition to defining a clinical variant of AH, it is important to assess its degree. An increase in SBP of 140–159 mm Hg and/or DBP of 90–109 mm Hg is regarded as moderate hypertension, while SBP ≥ 160 mm Hg and/or DBP ≥ 110 mm Hg is considered severe hypertension. BP 160/110 mm Hg and more is one of the criteria for severe PE (Russian Society of Cardiology 2018; Chulkov et al. 2020).

The management of such patients is carried out by doctors of several specialties at once, primarily therapists (general practitioners), physicians cardiologists and

obstetrician-gynecologists. Based on this, the problem of arterial hypertension in pregnant women is extremely significant in social and medical terms.

The aim of the study

To assess the level of knowledge and preferences of doctors in various regions of Russia regarding the diagnosis, management tactics and rational pharmacotherapy of arterial hypertension in pregnant women.

Materials and methods

A multicenter pharmacoepidemiological study was conducted in 2018–2021 using the anonymous questionnaire method among 411 doctors from 8 regions of Russia (Belgorod, Novosibirsk, Chelyabinsk, Sakhalin, Voronezh and Moscow Regions, Primorsky and Krasnodar Territories). The full name of the project was "The Study of Physicians' Knowledge of Gestational Hypertension" (PHYGEST Project); the name is copyright, it was not registered in the research registers on the international portals of clinical trials and in the Ministry of Health of the Russian Federation. Since different specialists treat hypertension in pregnant women in practical medicine, both therapeutic specialists and obstetricians-gynecologists took part in this study.

The original questionnaire included 7 open-ended questions. Doctors were asked not to use the Internet and other sources of information when filling out the questionnaire. When filling out the questionnaire, doctors were asked to indicate their place of work, specialty, work experience, and type of assistance provided (inpatient or outpatient). The answers to the questions were divided into categories "correct", "incorrect" and in a number of questions with an incomplete answer – "partially correct". All information entered into the questionnaires was entered into a spreadsheet and processed using Microsoft Excel applications.

The rationality of the choice of antihypertensive and other drugs, diagnostic criteria were assessed on the basis of the clinical recommendations in place at the time of the study. The changes that appeared in the new versions of the clinical guidelines for cardiologists in 2020 (Kobalava et al. 2020) and obstetricians in 2021 (Russian Society of Obstetrics and Gynecology 2021), and comparison with the current foreign recommendations are also discussed in the article, but they did not affect the assessment of the results obtained.

Results and discussion

The study included 411 physicians, of which about half (45%) were therapists (or general practitioners), 13% were cardiologists, 22% were obstetrician-gynecologists, and 20% were other physicians. According to the type of care they provided, the distribution was as follows: outpatient doctors – 47%, inpatient care – 44%, and 9% of specialists worked simultaneously on an outpatient basis and in a hospital. Work experience in the specialty was less than 5 years for 45% of doctors, from 5 to 10 years – for 15%, and over 10 years – for 40% of doctors. According to the territorial distribution, the most numerous group was doctors from Krasnodar Territory (24%), followed by Novosibirsk Region (20%), Belgorod Region (19%), Moscow and Moscow Region (12%), Chelyabinsk Region (12%), Primorsky Territory and Sakhalin Region (8% in total), and Voronezh Region (5%) (Fig. 1).

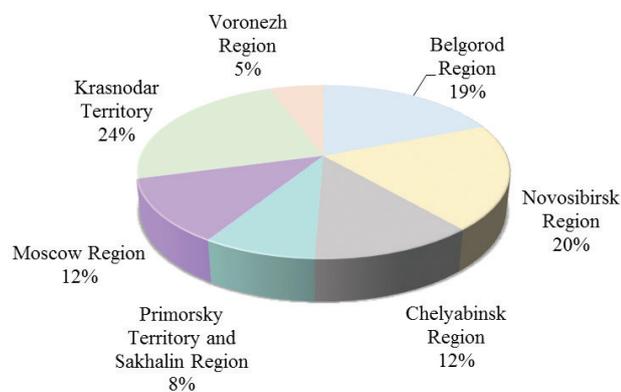


Figure 1. Share of participating regions in the PHYGEST study (N=411).

In question No. 1, the respondents were required to indicate at what level of blood pressure in pregnant women they would recommend treatment with antihypertensive drugs. According to the text of the RSC (Russian Society of Cardiology) clinical guidelines (Kobalava et al. 2020), women with CAH, if there is no target organ damage (TOD) and associated clinical conditions, the initiation of drug therapy is recommended at SBP ≥ 150 mm Hg or DBP ≥ 95 mm Hg; for all other forms of hypertension in pregnant women – at SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg. The American College of Obstetricians and Gynecologists recommends utilizing 140/90 as the threshold for initiation or titration of medical therapy for chronic hypertension in pregnancy (Tita et al. 2022), rather than the previously recommended threshold of 160/110 (ACOG 2019).

In our study, the majority of specialists indicated the SBP range of 140–149 mm Hg as the initial level for starting therapy; the second most popular range was the range that fits into the numbers of high normal BP: SBP – 130–139 mm Hg, which does not require therapy in most situations, according to clinical guidelines. The majority of physicians in the study (73.7%) indicated a SBP range of 140–149 mm Hg as a criterion for initiating antihypertensive therapy, a range of 130–139 mm Hg was indicated

by 19.2% of specialists, ≥ 150 mm Hg – by 6.3% and less than 130 mmHg – by 0.8% (Fig. 2).

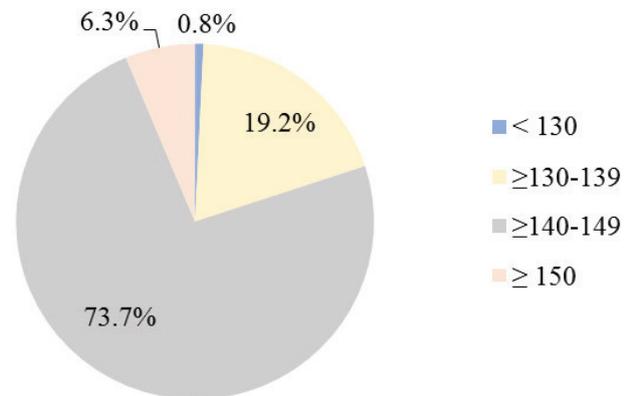


Figure 2. Initial level of starting antihypertensive therapy in pregnant women, according to a survey of doctors.

In question No. 2, the respondents were asked to indicate a level of blood pressure at which they would recommend hospitalization of pregnant women.

Pregnant women with SBP ≥ 170 and DBP ≥ 110 mm Hg are advised to be urgently hospitalized and this condition should be treated as a hypertensive crisis. This recommendation was introduced into practice in 2020 (Kobalava et al. 2020), before that the “critical” level of SBP was considered to be ≥ 160 mm Hg.

However, in this aspect, most doctors remain extremely wary and prefer to play it safe.

When analyzing the answers of doctors in our study, 5 groups of SBP ranges were identified, in which doctors considered it appropriate to recommend hospitalization of a woman (Fig. 3): up to 139 (3.7%), $\geq 140-149$ (31.0%), $\geq 150-159$ (19.9%), $\geq 160-169$ (32.9%), and ≥ 170 (12.5%) mm Hg, respectively.

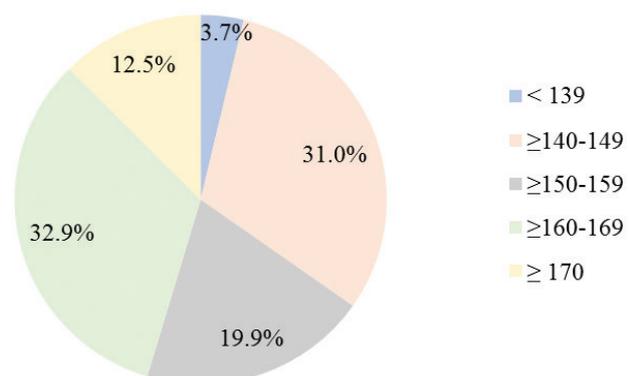


Figure 3. SBP levels requiring hospitalization of pregnant women, according to physicians.

Based on the data obtained, in most responses, the interviewed physicians suggested initiating antihypertensive therapy in pregnant women starting with a SBP level $\geq 140-149$ mm Hg (73.7%), while 50.9% of specialists are ready to hospitalize women as early as with a SBP in the range of 140-159 mm Hg. However, in accordance with the current classification, hypertension in pregnant women is regard-

ed as “severe” and hospitalization is recommended at SBP levels of 160 mm Hg or more and/or DBP levels of 110 mm Hg or more, with 32.9% of respondents sharing this view.

Thus, it was found that many doctors had increased alertness even to blood pressure figures that do not require inpatient treatment and, by and large, unreasonably recommend hospitalization.

In question No. 3, the respondents were asked to indicate which antihypertensive drugs they would prescribe for hypertension in pregnant women for emergency lowering of blood pressure, for planned therapy, etc. (Table 1).

The possibilities of antihypertensive therapy in pregnant women are very limited. According to clinical guidelines, the use of methyldopa and sustained-release nifedipine is recommended as oral drugs for emergency lowering of blood pressure (Kobalava et al. 2020). It is also recommended that clonidine be used in refractory hypertension therapy.

Table 1. Medicines for emergency lowering of blood pressure, planned treatment and others in pregnant women according to survey of doctors

Groups of drugs	Medicines for emergency lowering of blood pressure	Medicines for the planned treatment of hypertension	‘Other’ medicines for the treatment of hypertension
	%	%	%
Calcium antagonists	46.2	21.3	12.8
- nifedipine	97.2	–	–
Magnesium preparations	25.1	0.2	5.8
Centrally acting drugs	18.1	54.4	4.7
- methyldopa	74.1	97.6	–
- moxonidine	15.3	2.4	–
- clonidine	10.6	–	–
BB	3.0	20.6	64.0
Nitrates	2.8	0.2	–
ACE inhibitors	3.0	1.1	1.2
Diuretics	1.1	1.3	3.5
Peripheral vasodilators	0.2	0.2	–
Other drugs	0.6	0.2	2.3
Non-drug treatment	–	0.2	1.2
Consultation of a therapist	–	0.4	–
Phytotherapy	–	–	4.7

Sodium nitroprusside is rarely used if there is no effect from the above drugs and/or there are signs of hypertensive encephalopathy (Russian Society of Obstetrics and Gynecology 2016). For the treatment of pre-eclampsia with pulmonary edema, nitroglycerin is the drug of choice, and intravenous magnesium sulfate is recommended to prevent eclampsia and to treat seizures (Kobalava et al. 2020). It is also recommended to administer magnesium sulfate in the event of hypertension in a pregnant woman at the first stage of medical care, while it must be remembered that this drug is not an antihypertensive drug itself (Russian Society of Obstetrics and Gynecology 2016). At the same time, the introduction of magnesium sulfate as a planned therapy for moderate PE during pregnancy does not prevent the progression of PE. In severe resistant hypertension in pregnant women, the alpha-blocker urapidil is recommended with caution, which is prohibited in the

postpartum period during breastfeeding (Russian Society of Obstetrics and Gynecology 2021).

According to the results of the survey, the following data were obtained: for an emergency reduction in blood pressure, among the drugs of choice doctors most often indicated the group of calcium antagonists (46.2%), where nifedipine was mentioned in 97.2% of the answers and magnesium preparations ($MgSO_4$) – in 25.1%; centrally acting drugs (18.1% of the total) were represented by the following drugs: methyldopa (74.1%), moxonidine (15.3%), and clonidine (10.6%). The following groups of drugs were also presented: beta-blockers (BB) (bisoprolol, labetalol, propranolol) – 3.0%, nitrates (2.8%); as doe angiotensin converting enzyme inhibitors (ACE inhibitors) (3.0%), we note that this is an unsafe recommendation and an absolute contraindication during pregnancy; diuretics (1.1%), peripheral vasodilators (nitroprusside) (0.2%), other drugs (antispasmodics, analgesics (“andipal”, dibazol + papaverine – 0.6%), respectively, the latter appointment is also irrational and unsafe.

According to the current clinical practice for planned oral therapy, methyldopa should be used as the basic first-line drug (Russian Society of Obstetrics and Gynecology 2016, 2021; Kobalava et al. 2020), in case of ineffectiveness, sustained-release nifedipine should be used. The 2nd line drug is a representative of the BB group – metoprolol succinate (Russian Society of Obstetrics and Gynecology 2016). Reserve drugs for the treatment of hypertension, which are prescribed in case of ineffectiveness or poor tolerance of the main drugs, are bisoprolol, clonidine, verapamil, amlodipine, prazosin, hydrochlorothiazide, and furosemide. These drugs are likely to be prescribed after approval by a medical board, or a clinical pharmacologist or any other authorized specialist (Russian Society of Obstetrics and Gynecology 2016; Kobalava et al. 2020). Combination therapy is carried out in case of failure of monotherapy, and in many cases it will be more effective than any monotherapy (Kobalava et al. 2020). A rational combination is long-acting nifedipine in combination with BB (Russian Society of Cardiology 2018). A combination of both or any of these drugs with methyldopa is also possible and rational. If necessary, other reserve drugs are combined, starting with small doses. Thus, the authors have a successful experience of achieving the target values in chronic hypertension at the minimum dosages of the original drugs amlodipine and bisoprolol (“Norvask” and “Concor”) starting from the pre-gravid period and ending with successful control of blood pressure throughout pregnancy (Bontsevich et al. 2018).

According to our data, the group of centrally acting drugs (54.4%) (methyldopa (97.6%) and moxonidine (2.4%)) was the most frequently recommended for the planned treatment of hypertension in pregnant women among the surveyed doctors, followed by calcium antagonists (21.3%) (amlodipine, verapamil, nifedipine) and BB (20.6%) (labetalol, bisoprolol, nebivolol, atenolol, metoprolol). The other drug groups were as follows: ACE inhibitors (enalapril) (1.1%), diuretics (indapamide) (1.3%), nitrates (nitroglycerin) (0.2%), magnesium preparations ($MgSO_4$) (0.2%), peripheral vasodilators (prazosin) (0.2%), respectively, with 0.2% of the physicialns selecting a non-drug treatment. Doctors of non-therapeutic

specialties preferred the consultation of a therapist in 0.4% of cases, and the drug was incorrectly indicated in the list of antihypertensives - dabigatran (also included in the “other” group) – at 0.2%.

Also, as part of question No. 3 in the questionnaire, the doctors had the opportunity to write other drugs that they used in the treatment of hypertension in pregnant women. A total of 86 (n) such responses were collected. The main answers were again in this section, antihypertensive drugs from the class of the BB group (**metoprolol**, **bisoprolol**, **nebivolol**, **atenolol**) – 64.0%, calcium antagonists (**verapamil**) – 12.8%; in addition, doctors indicated magnesium preparations (5.8%), phytotherapy (motherwort preparation) – 4.7%, centrally acting drugs (**methylodopa** and **moxonidine**) – 4.7%, diuretics (**indapamide**, **triamterene**, **hydrochlorothiazide**) – 3.5%, ACE inhibitors (**captopril**) – 1.2% and non-drug treatment (1.2%), respectively.

In the “others” group (2.3%) represented by the anti-spasmodics, without specifying a specific drug and one answer “everything is possible” was also received. The authors of the questionnaires note that a number of these drugs are irrational and unsafe for use during pregnancy.

In question 4, the respondents were asked to indicate what target blood pressure they were trying to achieve in pregnant women with hypertension. There is no consensus on this issue in the scientific community. According to the text of some Russian clinical guidelines, the target level of blood pressure for pregnant women is <140/90 mm Hg (Kobalava et al. 2020). In this case, however, episodes of hypotension should be avoided so as not to impair placental blood flow.

According to the text of other recommendations (Russian Society of Obstetrics and Gynecology 2016), the dose of antihypertensive drugs should be selected so that the SBP values are in the range of 130–150 mm Hg and DBP – 80–95 mm Hg. Based on the numbers of initiation of antihypertensive therapy, target BP values in the treatment of CAH without TOD were <150/95 mm Hg, and in the treatment of GAH, preeclampsia, CAH with TOD – <140/90 mm Hg. The profile guidelines of the Canadian Society of Obstetricians and Gynecologists note that in moderate hypertension without comorbid diseases, antihypertensive drugs can be used to keep SBP from 130 to 155 mm Hg and DBP in the range of 80–105 mm Hg, while indicating a rather high strength of such recommendations – I-B (Aleksandrov et al. 2014).

When analyzing the responses of doctors in our study, 4 groups of the SBP range were identified with an interval of 10 mm Hg and the following data were obtained (Fig. 4): <120 (5.6%), 120–129 (42.1%), 130–140 (50.4%), and >140 (1.9%) mmHg.

Thus, the preferred target level of BP reduction according to the physicians’ survey was the range of 130–140 mm Hg, which is suitable for patients with GAH and CAH with TOD, but excessive for women with CAH without TOD.

In question No. 5, it was necessary to indicate whether the respondents prescribed any drugs to prevent the development of hypertension in pregnant women. Serious studies confirming the protective significance of such prescriptions were not found in the literature available to us. Clinical

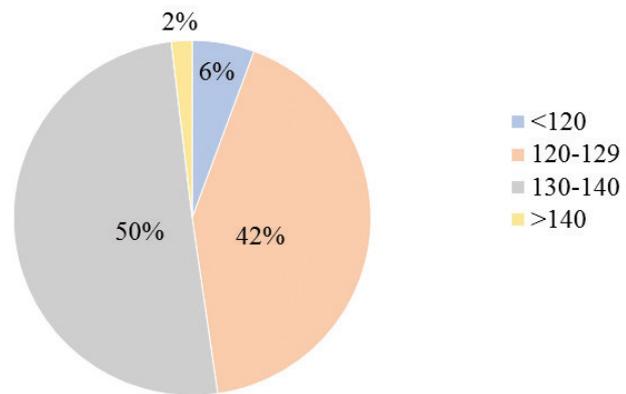


Figure 4. Target values of blood pressure in the treatment of hypertension in pregnant women according to the results of a survey of doctors.

guidelines do not discuss this approach either. However, “in conditions of real clinical practice”, doctors quite often make such prescriptions (according to our data, in 21.5% cases), the distribution of which was as follows: the group of antiplatelet agents (**aspirin**, dipyridamole) was preferred to be selected in 8.1% of cases, the group of BB (**nebivolol**) and calcium antagonists (**nifedipine**) were respectively chosen in 0.5% of cases each magnesium preparations in 2.2%, calcium preparations in 3.8%, centrally acting drugs (**methylodopa**) – 1.4%, sedatives (valerian, motherwort) – 2.9%, other drugs (in this group – cynara, **hypothiazide**, **vitamin D**, trioxazine are combined in equal proportion) – 1.0%, and, finally, non-drug treatment was preferred in 1.2% of cases. More than 3/4 specialists (78.5%) answered that they never prescribe additional drugs for the prevention of hypertension. The results of the answers are shown in Fig. 5.

In question No. 6, the doctors were asked to indicate any additional drugs prescribed by a specialist to pregnant women for any tactical considerations related to optimizing the management of hypertension in pregnant women (in order to improve blood pressure control, to improve prognosis; to prevent preeclampsia/preeclampsia, placental insufficiency, etc.).

At the same time, modern recommendations discuss such possibilities, but a rather limited list of drugs with one or another evidence base is presented. It is known that women with a high risk of PE for the purpose of its prevention are recommended to prescribe small doses (150 mg) of acetylsalicylic acid from the 12th week to the 36th week of pregnancy, provided there is a low risk of gastrointestinal bleeding (Russian Society of Obstetrics and Gynecology 2016; Daniel et al. 2017).

Of vitamins, it is recommended to prescribe oral **folic acid** during the first 12 weeks of pregnancy at a dose of 400 mcg per day; pregnant women at high risk of **vitamin D** hypovitaminosis are recommended to take oral **vitamin D** throughout pregnancy at a dose of 10 mcg (400 IU) per day.

A pregnant patient at low risk of beriberi is not recommended to routinely take a multivitamin. Of micro/macronutrients, calcium supplementation is recommended for pregnant women with low calcium intake (<600 mg per day) (Russian Society of Obstetrics and Gynecology 2016); taking iodine preparations (potassium iodide) should be

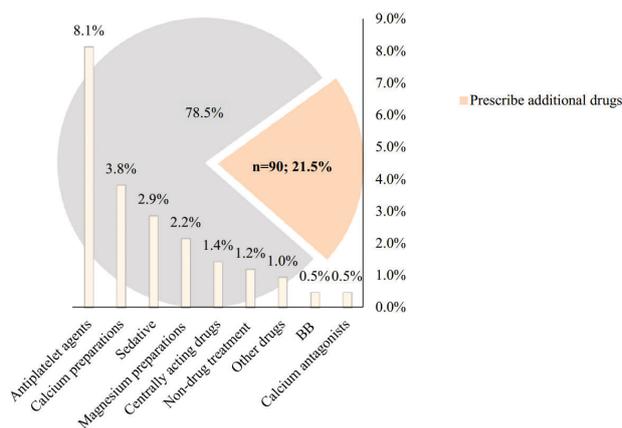


Figure 5. Prescribing any drugs to prevent the development of hypertension in pregnant women according to the results of a survey of doctors (n=90; N=418).

taken throughout pregnancy at a dose of 200–250 mcg per day (Russian Society of Obstetrics and Gynecology 2020).

In the answers of the respondents, the advantage remained with the answer option “prescribe additional drug” (54.5%); the sample included antihypertensive drugs, represented by groups of BB, alpha-blockers, calcium antagonists, *methyldopa*, diuretics (in total 6.3% of cases); herbal preparations (1.1%) represented by preparations “Chophytol” and “Canephron N”; antiplatelet agents (“*Trental*”, “*Aspirin*”, *dipyridamole*) – 27.6%; magnesium preparations (7.0%); calcium preparations (2.2%), iron preparations (1.1%); iodine preparations (0.9%); vitamin complexes and monopreparations of vitamins (*vitamin D*, *folic acid*, *vitamin C*) (in total 2.4%); antioxidants (2.4%) represented by drugs “*Mexidol*”, “*Actovegin*”; sedatives (*valerian*) (1.3%); the “other” group in total in 2.2% of cases, represented by the following answers – “*Riboxin*”, “*Meldonium*”, *diosmin*, planned therapy taken earlier, non-drug treatment and myotropic vasodilators. The results of the answers to question No. 6 are shown in Fig. 6.

When answering question No. 7 of the questionnaire, the respondents were tasked with briefly formulating a diagnosis, starting from the initial data of the hypothetical clinical case described in the question, which included the week of gestation, blood pressure figures, and protein levels in the urine.

The data obtained in the study are shown in Fig. 7. We give the correct answers to the following subcategories of this question:

In paragraph “a” with the initial data: Pregnancy 14 weeks, BP=150/100, proteinuria 0.01 g/L, the correct answer was the formulation of the diagnosis: CAH, moderate AH. In the category of “partially correct” answers, we included answers without specifying a degree of hypertension, but with the correct formulation of the clinical variant of hypertension during pregnancy.

In paragraph “b” with the initial data: Pregnancy 24 weeks, BP=160/110, proteinuria 0.01 g/L, the correct answer was the wording: GAG, severe hypertension. The category “partially correct” by analogy with point “a” included answers without specifying a degree of hypertension, but with the correct formulation of the clinical variant – GAG.

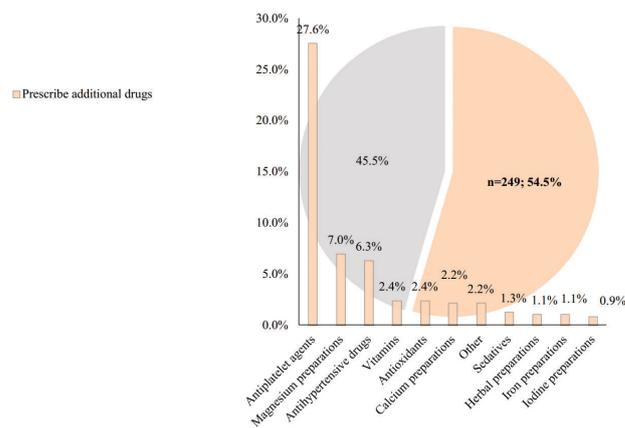


Figure 6. Prescribing any additional drugs to pregnant women with hypertension according to the results of doctors’ survey (n=249; N=457).

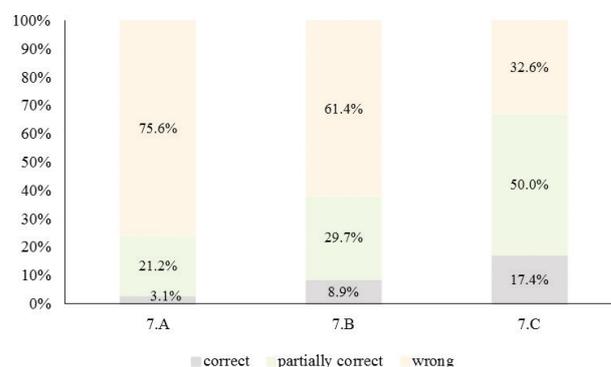


Figure 7. Formulation of the diagnosis for various types of hypertensive disorders in pregnant women based on the initial data from the results of doctors’ survey.

In paragraph “c” with the initial data: Pregnancy 34 weeks, BP=150/100, proteinuria 0.4 g/L, the correct answer was the wording: PE, moderate. The “partially correct” category included answers without indicating a degree or indicating “severe” degree instead of “moderate” degree, but with the correct wording of the clinical variant of hypertension.

In paragraph “a”, among the wrong answers (75.6%) there were the following wordings – “Hypertension associated with pregnancy”, “Hypertension of pregnant women”, “Hypertension”, “Gestosis”, “Newly diagnosed hypertension”, “Gestational nephropathy”, “Early gestosis”, “Toxicosis”, “Neurocirculatory dystonia of hypertonic type”, “Mild AH”, “Symptomatic AH”, and “Secondary AH”.

In paragraph “b”, among the wrong answers (61.4%) there were the following wordings – “Preeclampsia”, “Hypertension”, “Preeclampsia of pregnant women”, “Late gestosis”, “Preeclampsia of an average degree”, “Nephropathy of the 2nd stage”, “Moderate preeclampsia”, “CAH”, “Eclampsia”, and “Secondary AG”.

In paragraph “c”, among the wrong answers (32.6%) there were the following wordings – “GAG”, “Eclampsia”, “Hypertension”, “AH 2nd degree”, “Pyelonephritis”, and “Nephropathy of the 2nd stage”.

In total, for 3 points of question No. 7, the percentage of correct (and partially correct) answers was 43.5%, and incorrect ones – 56.5%, respectively. The highest percentage of incorrect answers (75.6%) was given in point “a”

and the highest percentage of correct answers (67.4%) was given in point "c".

The maximum number of errors was made precisely in the formulation of the diagnosis – CAH and the indication of a degree of increase in blood pressure.

Conclusion

Thus, according to the results of our study, the initial choice of antihypertensive therapy for AHT in pregnant women in some cases does not correspond to the current clinical recommendations in Russia. Target and

critical levels of blood pressure are also often presented inaccurately by physicians. The knowledge of doctors regarding the formulation of the diagnosis is also insufficient. The awareness of physicians of the issues of hypertension in such a category of people as pregnant women, despite the prevalence of pathology and the availability of relevant clinical recommendations, is not satisfactory enough, which, in our opinion, requires special attention to this issue and justifies the need for an in-depth study of this topic in postgraduate programs and continuous education programs and the introduction of additional public educational programs for doctors from different regions.

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