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Management in pregnancy complicated with chronic hypertension

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SUMMARY

Chronic hypertension concerns approximately 1% of pregnant women. In most cases, it is primary hypertension. In the remaining cases, it is usually associated with renal, vascular or endocrine disorders. Clinical assessment of a patient with hypertension consists in the identification of the cause of this condition, evaluation of cardiovascular risk factors and detection of target organ complications. The aim of treatment in patients with arterial hypertension is to control blood pressure to the value of 140/90 mmHg. That is why reliable blood pressure measurements are a crucial element of both diagnosis and monitoring of antihypertensive therapy. Treatment should include both non-pharmacological methods and, at the next stage, implementation of medications that can be used during pregnancy. Various priorities of antihypertensive therapy, associated with the necessity to include benefits for both the mother and fetus, and the lack of randomized trials comparing antihypertensive medications used during pregnancy evoke discussions among perinatologists and cardiologists. The greatest benefits for both pregnant women and children born of pregnancies complicated with arterial hypertension are observed when physicians of all specialties cooperate and share information and experience.
The paper presents current guidelines concerning diagnosis, monitoring and chronic treatment of arterial hypertension in pregnancy.
Key words: chronic hypertension; pregnancy

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INTRODUCTION

Arterial hypertension is a significant mortality risk factor in the global population despite intensively implemented diagnostic and therapeutic interventions. This can result from a long asymptomatic period, neglecting initial symptoms and the variety of causes affecting hypertension. Primary arterial hypertension which begins as harmless regulation impairment, usually with asymptomatic onset, can result in a chronic disease with progressive and insidious course and frequently tragic consequences. This disease results from the combination of genetic, environmental, lifestyle-related as well as mental and somatic factors [1]. Secondary arterial hypertension denotes a condition in which elevated blood pressure is due to a clear, single cause which can be identified with given diagnostic methods and corrected. Since primary arterial hypertension is common, both forms of hypertension, i.e. primary and secondary, can develop simultaneously. Moreover, primary hypertension can develop into secondary hypertension (e.g. atherosclerotic renal artery stenosis or renal parenchymal hypertension in renal insufficiency) [2].

Clinical assessment of a patient with hypertension consists in the identification of the cause of hypertension, evaluation of cardiovascular risk factors and detection of target organ complications. It must be emphasized that the risk of these complications can exist when RR values are within the normal range, particularly when masked or white-coat hypertension occurs. Particular attention must be paid to the history of non-specific symptoms, such as headaches, weakness or increased sweating. These symptoms can be particularly manifested in chronic hypertension during pregnancy.

CHRONIC HYPERTENSION IN PREGNANCY

Chronic hypertension in pregnancy is defined as arterial hypertension existing before pregnancy or diagnosed in a pregnant patient up to week 20 of gestation and persisting for more than 42 days after labor. The classification of chronic hypertension in pregnancy based on blood pressure measurements is not different from the general classification established by the ESC/ESH in 2013 [3].

Category	SBP		DBP
Optimal blood pressure	< 120	and	< 80
Normal blood pressure	120-129	and/or	80-84
High normal blood pressure	130-139	and/or	85-89
Stage 1 hypertension	140-159	and/or	90-99
Stage 2 hypertension	160-179	and/or	100-109
Stage 3 hypertension	≥ 180	and/or	≥ 110
Isolated systolic hypertension	≥ 110	and	< 90

It must be remembered that this group of patients is not homogeneous. It can include women with preexisting white coat hypertension or masked hypertension in whom no diagnosis or treatment have been made, as well as those in whom hypertension has been previously identified and treated or in whom only prophylactic measures have been implemented (e.g. dietary salt intake reduction, weight loss, limiting alcohol consumption, smoking or drug intake). In both these patients and women who plan pregnancy, attention must be paid to external (physical and mental activity, addictions and improper diet) and internal factors (function of the renin–angiotensin–aldosterone system, hypothalamic–pituitary–adrenal axis, autonomic system and melatonin) that can affect blood pressure rhythm [4].

In patients with arterial hypertension, it should be attempted to reduce blood pressure below 140/90 mmHg. However, in high-risk patients (with diabetes, history of stroke or myocardial infarction, renal insufficiency or proteinuria), blood pressure values should not exceed 130/80 mmHg. Moreover, it is emphasized that microalbuminuria is an early sign of renal damage in the course of arterial hypertension [5].

Reliable blood pressure measurements are a crucial element of both diagnosis and monitoring of antihypertensive therapy. Due to a gradual reduction in venous return with the course of pregnancy, blood pressure should be measured in a sitting position or left lateral position. The diagnosis of hypertension during pregnancy with the use of 24-hour ambulatory blood pressure monitoring (ABPM) is superior to office measurements due to its higher prognostic value. The use of ABPM as a significant tool in hypertension control in the pregnant and in women intending to become pregnant enables one to establish better cooperation, obtain reliable measurements and improve treatment outcomes [6]. 24-hour monitoring enables the assessment of drug efficacy or evaluation of its dose, which is significant in the pregnant in terms of potential and possible adverse effects of pharmacotherapy. For this purpose, the smoothness index is used. It is defined as the reverse of the ratio of the hourly differences between ABPM conducted at baseline and during treatment. This index includes all blood pressure reductions during 24 hours between baseline and a point during treatment [7]. According to the ESH/ESC, if ABPM is not possible, blood pressure values obtained in self-measurements are also very important.

However, not only measurement values should be considered during treatment, but also various profiles of different patients:

- pregnant women with normal 24 hour BP values associated with the physiological drop in the second trimester. Pregnancy is accompanied by a reduction in systemic vascular resistance. This is caused by increased production of vasodilatory substances, such as nitric oxide or prostacyclin and hormones (progesterone, estrogens, prolactin). Vascular myocytes are less sensitive to vasoconstrictors. That is why arterial pressure is observed to decline gradually with its maximum reduction by 10–20% in the middle of pregnancy. Moreover, decreased pulmonary vascular resistance is noted;
- pregnant patients with arterial hypertension observed only in the doctor's office as an "early form" of hypertension with slightly elevated BP values during the day and excessively decreased during the night, so-called white coat hypertension (isolated office hypertension);
- pregnant patients with elevated BP values outside the clinical settings compared with those observed in the doctor's office or cli-

nic, so-called masked hypertension – isolated ABPM hypertension which has not been detected or treated earlier. It is frequently associated with asymptomatic target organ complications as well as the risk of diabetes and persistent hypertension;
- patients with primary hypertension with increased 24-hour values and normal nightly decline or drug-induced decline;
- patients with increased 24-hour values and excessive nightly decline (frequently secondary forms of hypertension).

It must be underlined that, in the four last groups, asymptomatic complications, such as left ventricular hypertrophy and increased risk of stroke and cardiac infarction, can be more common. This also concerns metabolic risk factors of newly occurring diabetes [2,8]. Because patients with white coat hypertension frequently receive treatment, lowering blood pressure values leads to decreased incidence of cardiovascular events.

Patients with newly diagnosed arterial hypertension before the 20th week of pregnancy require systematized basic clinical assessment in order to determine whether hypertension is primary or secondary. The basic assessment should include medical history focused on the cardiovascular system, physical examination and laboratory tests. A thorough medical interview should concern diseases occurring in close relatives (parents, siblings), patient's lifestyle and psychosocial environment, history of or current diseases with particular attention paid to cardiovascular conditions, diabetes, asthma, kidney and urinary tract diseases, gout or hyperlipidemia, endocrine disorders and sleep disorders. In the case of hypertension before pregnancy, the following must be considered: duration of the condition from the diagnosis, results of previous measurements (ambulatory and 24-hour measurements), an increase in BP during pregnancy, earlier antihypertensive treatment and symptoms indicating secondary hypertension [9].

The minimum range of tests that need to be conducted is a debatable issue. The diagnostic process should progress from the simplest to the most complex examinations. The younger the patient and the higher the BP as well as the faster the development of hypertension, the more detailed the diagnostic process [9]. Basic diagnostic tests should include: blood tests (hemoglobin, hematocrit, platelet count, fasting glucose, serum lipid level, sodium and potassium concentrations, creatinine level including GFR and uric acid concentration), urinalysis (glucosuria, albuminuria, protein in 24-hour urine collection and morphology) and ECG (heart rhythm, possible heart ischemia and left ventricular hypertrophy) [10,11]. Each patient must have an eye fundus examination, including a classification of retinal changes in the course of hypertension.

If secondary hypertension is suspected, an extended diagnostic process can be indicated. It should include the most typical causes of secondary hypertension, in particular renal artery stenosis, hyperaldosteronism, thyroid diseases and pheochromocytoma. In patients planning pregnancy, the influence of previously used contraceptives on BP value changes must be considered.

Modern antihypertensive therapy should take into account the needs of a given patient and enable rapid control of the circadian rhythm with no adverse effects. Not only does this task require an effective BP reduction, but also treatment of all coexisting risk factors. A considerable majority of pregnant patients with preexisting hypertension have mild to moderate hypertension and carry a low risk of cardiovascular events during pregnancy. Patients with preexisting hypertension and normal renal function have good prognosis and are candidates for non-pharmacological treatment [12]. Such management should also be considered in patients with systolic blood pressure of 140–150 mmHg or diastolic BP of 90–99 mmHg measured in office conditions and ABPM values that do not exceed these levels. In such cases, close monitoring, reduced physical exercise and rest on the left side are recommended. By contrast with the recommendation of dietary salt intake reduction in hypertension without pregnancy, pregnant patients should not reduce it considerably since salt deficiency can enhance hypovolemia and secondarily deteriorate uterine vascularity. So-called salt-sensitive hypertension is an exception [11]. Furthermore, although body weight reduction is helpful in reducing BP, it is not recommended in pregnant obese patients. Such management could be associated with lower birth weight and subsequent worse growth of infants [11]. In the case of a positive history of prediabetes (<28th week of pregnancy), low prophylactic doses of acetylsalicylic acid are recommended (75–100 mg daily). It should be taken in the evening starting before conception or from the detection of pregnancy but before week 16. This treatment should continue to week 34 of gestation [12]. Such management is also recom-

mended in women with hypertension during their previous pregnancies, chronic renal insufficiency, autoimmune diseases, such as systemic lupus erythematosus or antiphospholipid syndrome, type 1 or 2 diabetes, persistent hypertension or with more than one moderate risk factors of preeclampsia (first pregnancy, age $\geq$ 40, interval between subsequent pregnancies >10 years, BMI $\geq$ 35 kg/m2 at the first visit, family history of preeclampsia or multiple pregnancy) [3].

PHARMACOTHERAPY FOR CHORNIC HYPERTENSION IN PREGNANCY

Pharmacotherapy for chronic hypertension in pregnancy is indicated when blood pressure is 150/95 mmHg [13]. Pregnant patients with chronic hypertension and concomitant target organ complications should start pharmacological treatment with BP value of 140/90 mmHg. Pharmacological management should be combined with lifestyle changes every time target organ complications are identified or in coexisting diabetes. If subclinical target organ changes occur (particularly microalbuminuria or overt proteinuria) pharmacotherapy should begin in patients with high normal blood pressure. Treatment should start with the lowest possible doses in order to minimize adverse effects. Patients without nightly BP drop or with excessive morning BP elevation should consider a change of the time at which an antihypertensive drug is used. If symptoms of orthostatic hypotony are observed during antihypertensive therapy, BP should also be measured in the standing position [14].

In the case of previous usage of angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists, pharmacotherapy should be discontinued instantly. Moreover, diuretics are also contraindicated. If BP values associated with its physiological drop are normal, non-pharmacological management is sufficient. If, however, BP values exceed the limit values, a different antihypertensive therapy should be implemented as soon as possible since fetal exposure to ACE inhibitors in the second and third trimesters of pregnancy is a known fetotoxic factor (renal dysfunction, arterial hypotension, hyperkalemia). Moreover, prolonged exposure to thiazides and indapamide in the third trimester of gestation can reduce maternal plasma volume, thereby leading to decreased placental flow and intrauterine fetal growth restriction. Moreover, rare causes of hypoglycemia and thrombocytopenia have been observed in neonates [15,16]. Drugs that are absolutely contraindicated for chronic use include atenolol and prazosin. There are no data about new generation medications, such as eplerenone (a selective aldosterone blocker) in pregnant women. Animal studies carried out so far have not shown adverse effects concerning pregnancy, fetal and embryonic development, labor or neonatal development. According to the manufacturer, this agent should be used in the pregnant with caution. It is not known whether this drug enters breast milk.

Still, the medication of choice in long-term therapy of chronic mild to moderate hypertension in pregnancy is methyldopa [3]. This centrally acting agonist for alpha 2-adrenergic receptors is highly effective and safe. Dosage in outpatient conditions should not exceed 2 g/24 hours, and the maximum admissible daily dose in special situations is 4 g. Moreover, labetalol (alpha- and beta- blocker) is characterized by similar efficacy. Its advantages include the possibility of intravenous administration in cases of high blood pressure. However, this drug has been unavailable on the Polish market for a long time. Due to additional receptor properties, beneficial effect on metabolic parameters and endothelial function, beta-blockers can be indicated. However, since they can cause fetal growth restriction (if used in the second and third trimesters of gestation), they should be administered with caution [17]. It must be remembered that beta-blockers can conceal signs of acute hypoglycemia and seemingly eliminate signs of hyperthyroidism. Their abrupt discontinuation can exacerbate hyperthyroidism, and even cause thyrotoxic crisis. Drugs of this group that can be administered include: acebutolol, metoprolol and pindolol. Metoprolol (50–400 mg daily) is the most common. It can be used from the second trimester but cannot be combined with verapamil due to the risk of severe bradycardia. Second-line medications are calcium channel blockers (extended release nifedipine used orally at a maximum daily dose of 120 mg or intravenous isradipine). These drugs can be used in emergency situations, hypertension with preeclampsia and in hypertensive crisis [18,19]. Verapamil (480 mg daily in chronic treatment) is a calcium antagonist that is safe during the entire pregnancy. It can be an alternative for women with hypertension treated before pregnancy since it

does not impair organogenesis. It must be remembered, however, that it also has a relaxing effect on the myometrium. The usage of a full dose can result in contractile activity inhibition during labor, thus resulting in a necessity to conclude pregnancy with a cesarean section. To date, it has been believed that due to potential synergism of magnesium sulfate and calcium channel blockers, these two agents should not be used simultaneously, particularly in emergency situations (risk of maternal acute hypotony and fetal hypoxia). The latest guidelines of the Society of Obstetricians and Gynaecologists of Canada from 2014 allow their combination [10].

Certain authors claim that pharmacological treatment of mild chronic hypertension in pregnancy decreases the incidence of severe hypertension (>170/110mmHg) [20]. However, with low risk of maternal complications when maintaining optimal or normal BP values, it is recommended to keep BP within the high normal range without implementing intensive pharmacological treatment. Fetal risks associated with drug-induced hypotony that can decrease uteroplacental blood flow are considerably higher [21].

Pregnant women with blood pressure that exceeds 170/110 mmHg should be hospitalized. It must be remembered that an abrupt BP rise can induce arrhythmia in the mother, cardiac asthma (leading to pulmonary edema) and angina. In such a case, the selection of an antihypertensive drug and the route of its administration depend on the expected term of delivery and mortality risk of both the woman and fetus. When there are no concomitant symptoms, recommended drugs are labetalol, which can be used intravenously, as well as oral methyldopa or nifedipine. Intravenous hydralazine is no longer a medication of choice. Moreover, urapidil can be used in emergency situations and sodium nitroprusside (in a continuous intravenous infusion at a dose of 0.25–5.0 μg/kg/min) can be administered in hypertensive crisis. A sudden increase in blood pressure with simultaneous pulmonary edema is an indication for nitroglycerin use (a continuous intravenous infusion at a maximum dose of 100 μg/min at an initial rate of 5 μg/min, gradually increased every 3–5 minutes). Magnesium sulfate remains a drug of choice in treating convulsion attacks and eclampsia.

Arterial hypertension is common in the postpartum period. During the first several days after delivery, blood pressure increases, which can prolong hospitalization. All antihypertensive drugs enter breast milk, but most of them are detected in very low concentrations. Propranolol and nifedipine are exceptions (their breast milk concentrations are comparable to serum levels). Antihypertensive treatment can be discontinued for several months in breastfeeding women with mild arterial hypertension on condition that BP is carefully monitored. The first-choice medication is methyldopa. However, it should be used with caution in the postpartum period due to the risk of depression. Breastfeeding women can also use beta-blockers, but they are expected to affect the breastfed child. Contraindicated medications include ACE inhibitors and angiotensin antagonists due to their harmful effects on the neonate's kidneys, and diuretics since they inhibit lactation.

CONCLUSION

Arterial hypertension in pregnancy remains the major cause of maternal, fetal and neonatal mortality and morbidity both in developing and highly industrialized countries. It is the most common cardiac disorder that complicates pregnancy. Delaying motherhood, commonness of assisted reproductive technology and greater number of multiple pregnancies will cause a constant increase in the percentage of women with chronic arterial hypertension. On the other hand, a global problem of overweight and obesity in young individuals, the lack of physical exercise and poor dietary habits result in the fact that arterial hypertension with all its target organ complications develops at young age. In spite of considerable progress of perinatal medicine, such patients will still be a challenge for an obstetrician and physicians of various specialties.

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