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Topic: **«Pregnancy-Related Hypertension: Incidence, Outcomes»**

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CONTENTS

LIST OF CONDITIONAL ABBREVIATIONS

AH – hypertension;
ACE – angiotensin-converting enzyme;
ARB - angiotensin II receptor blockers
CCD - Calcium channels blocker;
CHD – coronary heart disease;
CKD – chronic kidney disease;
CVD – cardiovascular diseases;
BP - blood pressure;
BB – β- blocker;
BMI - body mass index;
DBP – diastolic blood pressure;
DM – diabetes;
DOAC – (direct oral anticoagulant);
GWAS – genome-wide association studies
HR – heart rate;
RF – risk factors;
SBP – systolic blood pressure;

INTRODUCTION

Actuality of theme. Changes related to pregnancy affect the entire female body. The cardiovascular system is no exception. It is known that during pregnancy new requirements are added to the cardiovascular system associated with weight gain of women, uterus, placenta, fetal growth, changes in uteroplacental circulation [1, 11]. Vessels during pregnancy are affected by changes in hormonal background, central nervous system tone, increased circulating blood volume, increased diaphragm height, increased intra-abdominal pressure and changes in heart position [10, 19]. All efforts of the body are aimed at improving blood circulation in the uterus and placenta. Therefore, it is not surprising that the restructuring of the mother's body can lead to the development of such pathologies as preeclampsia or late preeclampsia, which are manifested by increased blood pressure (BP), edema and the presence of protein in the urine [6, 17, 20]. Preeclampsia can become a separate disease or develop on the background of pre-existing hypertension (AH).

Hypertension is a serious threat to women and fetuses, because there is an additional burden on all organs and systems [3]. The main complications of pregnancy with blood pressure are the risk of miscarriage (27%), placental insufficiency, preeclampsia, premature detachment of the normally located placenta, multiorgan failure and disseminated intravascular coagulation syndrome [7, 33, 37]. Subsequently, the risk of eclampsia (25-27%), stroke, and dangerous bleeding in the postpartum period increases in childbirth [30, 39].

Hypertensive disorders in pregnant women according to the European Society of Cardiology are the most common complications, which occur in 5-10% of cases and remain the leading cause of morbidity and mortality among mothers, fetuses (4%) and newborns [16, 18, 21].

The main task of the doctor is to establish the threat of hypertension, multiorgan and placental insufficiency as soon as possible and to prescribe adequate treatment [45, 49, 51]. Prevention, prevention and treatment of hypertension with its possible consequences during pregnancy has some difficulties, as the choice of drug pharmacotherapy is very limited due to the impact on the baby and the mother [58].

Scientific developments and many years of experience of doctors prove that the main therapy for pregnant women with hypertension is to adhere to a protective regime and nutrition [55]. In addition, it is rational to prevent pregnancy complications, especially in the early stages [23].

The purpose of the work:

Analyze the causes, possible consequences of complications for women and fetuses associated with the development of hypertensive disorders during pregnancy and summarize possible ways of drug therapy.

Task:

1. To determine aspects of the etiopathogenesis of hypertension in pregnant women.
2. Analyze the risk factors for complications of hypertension in pregnant women
3. Evaluate laboratory and experimental studies during pregnancy
4. To generalize recommendations of possible ways of prevention and medical correction of hypertension of pregnant women.

Object of study*:* arterial hypertension of pregnant women.

Subject of study:

Consequences and possible ways to correct hypertension during pregnancy.

Research methods:

Analytical, general clinical, clinical and laboratory.

Scientific novelty.

The master's thesis identifies risk factors for the development of hypertension in pregnant women. Recommendations on diagnostic methods, prevention measures and drug therapy of hypertensive conditions in pregnant women are analyzed.

Approbation of results.

According to the results of the study, abstracts were published at the following conferences:

The practical significance of the results obtained.

The results of the analysis of the risk of mortality and morbidity in pregnant women with hypertension and comorbid conditions allow specialists in the field of

therapy to increase the effectiveness and safety of treatment, as well as prevention of complications in this group of patients.

SECTION 1 LITERATURE REVIEW

Human life is the most precious thing we have in the world. Preservation and comprehensive care of pregnant women and women in labor is the most important task of all medical and pharmaceutical professionals. For most women, pregnancy is a natural process, but sometimes there may be various deviations from the normal course of pregnancy. There is a "pregnancy risk group" - women with hypertension, heart disease, varicose veins and more. In many respects, expectant mothers need qualified medical support from the first weeks of pregnancy in order to bear and give birth to a healthy baby with their own health preserved [2, 43].

1.1 Definition, epidemiology, classification of arterial hypertension. Cardiovascular risk factors for hypertension

Hypertension is a polyetiological disease that occurs due to the interaction of harmful environmental factors (risk factors) and genetic (hereditary) factors. Hypertonic disease is an outdated term, which means an increase in excess blood pressure in the vascular bed since the 1990s is not used in medical practice, instead the term is recommended to use the term *hypertension* [47].

Hypertension occupies one of the leading places among the pathologies of the cardiovascular system and leads to significant disorders of the body - loss of ability to work, disability and significant economic losses [40].

Despite the current level of scientific research to date, the cause of hypertension (essential form), which accounts for about 95%, has not yet been established [12, 13]. The classical etiopathogenesis of this pathology includes several theories of arterial hypertension. Among them are the neurogenic theory, where the main role in the development of the pathological process is played by the CNS. According to the volume-salt theory, when the excretory function of the kidneys is initially impaired due to the delay in the body of sodium and water, there is an increase in cardiac output (VOC) and circulating blood volume (CBV). Genetic defects can contribute to hypertension due to disruption of various chains of blood pressure regulation -

transmembrane movement of Na and Ca ions, excessive production of pressors (or depressant deficiency), increased sensitivity of receptors to their action. The mechanism of regulation of Na metabolism, nervous regulation of arterial pressure, renin-angiotensin-aldosterone system is broken, rheological properties of blood change [32].

As a rule, before the appearance of various complications, hypertension often occurs without any symptoms, and its only manifestation is an increase in blood pressure [24, 25]. The first complaints of patients appear after the defeat of target organs [72].

Scientists estimate that 1.28 billion adults aged 30-79 are hypertensive worldwide, two-thirds of whom live in low- and middle-income countries. The WHO emphasizes that hypertension is most common in the African region (27%), and least - in the American region (18%) [13, 14].

Approximately 46% of people do not suspect the presence of pathologically high levels of blood pressure. Less than half (42%) of hypertensive patients adhere to treatment, undergo diagnostic procedures and listen to the doctor's recommendations for lifestyle changes. This contributes to the fact that every fifth (21%) adult hypertensive person controls the disease, realizing that hypertension is one of the leading causes of death worldwide.

Reducing the prevalence of hypertension by 33% in the period from 2010 to 2030 is one of the global goals in the fight against non-communicable diseases [60].

With each stroke, the heart throws blood into the vessels, while the pressure on the walls of the vessels. Because blood pressure is subject to some fluctuations - depending on the time of day or physical activity - long-term monitoring is needed to detect pathologies.

Blood pressure is described by two indicators. The first indicator (systolic pressure) is the pressure in the blood vessels at the time of compression, or contraction, of the heart muscle. The second indicator (diastolic pressure) is the pressure in the vessels at the moment when the heart is at rest between two contractions. Excessive pressure in the vessels leads to a loss of elasticity of the artery walls over time and a

gradual decrease in the supply of blood and oxygen to the heart muscle. Hypertension is very dangerous because it can lead to heart attacks, strokes, kidney failure and instant death.

Hypertension (AH) is persistently elevated systolic (SBP) and / or diastolic (DBP) blood pressure (BP).

AH is an increase in SBP to 140 mm Hg. Art. and above and / or DBP up to 90 mm Hg. Art. and above, if such an increase is stable (confirmed by repeated measurements of blood pressure at least 2-3 times on different days for 4 weeks.) Hypertension (essential hypertension or primary hypertension) is an elevated blood pressure in the absence of an obvious cause.

Primary hypertension.

Primary hypertension can be said when high blood pressure has no underlying disease as the cause. We can say that high blood pressure exists "by itself". This form of hypertension can be caused by various factors, but the exact cause is unknown.

Risk factors for the development of primary hypertension include genetic predisposition, obesity, alcohol consumption, lack of physical activity, smoking, age, potassium deficiency and high salt intake. In women, hypertension can also be associated with the onset of menopause, changes in hormonal background, abnormal pregnancy.

Hypertension in combination with type 2 diabetes, obesity and high cholesterol is a metabolic syndrome that significantly increases the risk of stroke [49, 50].

Secondary hypertension.

Secondary hypertension is always the result of another disease, such as kidney and vascular disease, metabolic disorders, and so on. In addition, some medications, such as birth control pills or rheumatism medications, can increase blood pressure. That is, secondary hypertension (symptomatic) is hypertension, the cause of which can be identified.

In 2018, the American College of Cardiology [American College of Cardiology (ACC)] and the American Heart Association [American Heart Association (AHA)] on the diagnosis, treatment, control and prevention of cardiovascular disease

published updated guidelines for the assessment of high blood pressure (BP). The recommendations of the ISH (International Society of Hypertension - ISH) adapted the standards, taking into account the differences between optimal health care with scientifically sound standards and the provision of health care based on basic care in the minimum standard of care with limited resources. Updated recommendations are relevant [9, 19].

The updated classification of hypertension, which is actively used in the world, and the criteria are given in Table 1.1.

Table 1.1

Classification of hyprtension

Category	**Blood pressure levels, mm Hg Art.**	
	SBP	**DBP**
Normal blood pressure	<130	<85
High normal blood pressure	130–139	85–89
AH stage I	140–159	90–99
AH stage II	≥160	≥100
Criteria of hyprtension		
Office blood pressure (clinical, measured in the doctor's office)		≥140 і/або ≥90
Ambulatory control of AH	24-hour average	≥130 and/or ≥80
	Daily average value	≥135 and/or ≥85.
	Night time / sleep	sleep ≥120 and/or ≥70
Self-monitoring of AH		≥135 and/or ≥85

It is known that in hypertension there is a risk of additional cardiovascular factor or factors. Risk factors include complicated family history, diabetes (15–20%), impaired lipid metabolism (30%), obesity (40%), hyperuricemia (25%), metabolic syndrome (40%), sedentary lifestyle, and sometimes even psychosocial or socio-economic factors. Cardiovascular risk according to the recommendations is assessed by measuring blood pressure fluctuations and additional risk factors according to the simplified classification (Table 1.2)

Table 1.2

Simplified classification of cardiovascular risk

Cardiovascular risk factors	**Highly normal CBP 130–139 mm Hg. DBP 85–89 mm Hg.**		**AH I degree CBP 140–149 mm Hg. DBP 90–99 mm Hg.**	**AH of the II degree CBP ≥160 mm Hg. DBP ≥100 mm Hg.**	
There are no cardiovascular risk factors	Low		Low	Moderate	High
1 or 2 risk factors	Low		Moderate	High	
≥3 risk factors	Low	Moderate	High	High	
Target organ damage, chronic kidney disease (CKD) stage III, diabetes, cardiovascular disease	Low		High	High	

Necessary actions of the doctor to diagnose hypertension (2020)

Required:

1) The doctor or nurse performs measurements on the patient's shoulder with a spring sphygmomanometer using the auscultatory method or electronic device. Electronic devices using the auscultatory or oscillometric method are also used. Measurement of blood pressure at each visit to the doctor in standard conditions at least 2 times during the reception. At the first treatment blood pressure is measured on both hands. When a difference in the level of blood pressure in the hands is detected, a hand with a higher blood pressure is used for further measurements. Norm AT - 120/80.
2) Conducting a medical examination of all patients: physical examination, assessment of neurological status, ophthalmoscopy of the fundus of patients with SBP more than 160 mm. rt. Art. and patients with ophthalmic and neurological symptoms.

3) Laboratory tests: general analysis of blood, urine, determination of glycemia, creatinine - to conduct all at the initial treatment. If it is impossible to perform research in primary care facilities, you should be referred to a secondary care facility.
4) ECG registration in 12 leads.
5) Determination of risk factors and preliminary assessment of overall cardiovascular risk.
6) In case of secondary hypertension, resistant hypertension, hypertension in patients under 40 years of age, pregnancy with hypertension - referral for examination to secondary care facilities.

Some people (women) have a rise in blood pressure during a doctor's or nurse's measurement. This phenomenon is called the **white coat effect**. In this situation, you need to assess blood pressure outside the doctor's office.

Desired actions:

1. Laboratory tests: determination of ALT, TG, microalbuminuria, the level of total cholesterol, calculation of GFR by the Cocroft-Golt formula.
2. Instrumental examinations: ultrasound of the heart (echocardiography, Doppler-CG), ultrasound of extra cranial vessels of the neck, ultrasound of the kidneys.

Clinical blood pressure measurements should be performed at each visit to the doctor. They are the basis for the diagnosis of hypertension and evaluation of the effectiveness of antihypertensive treatment, and are also used to assess the overall cardiovascular risk [4, 5].

Global guidelines (both European and American) also emphasize that physicians in their clinical practice should use more than just office or clinical blood pressure (BP) measurements to diagnose and control hypertension. It is necessary to put into practice outpatient blood pressure measurements and the limit values (in the table below), according to which hypertension will be diagnosed, using outpatient 24-hour monitoring or home monitoring of blood pressure [22, 34].

The aim of treatment of patients with hypertension is to achieve the maximum reduction of the total risk of cardiovascular complications by achieving and maintaining for all categories of patients with hypertension a single target blood pressure with office measurement <140/90 mm Hg (emphasizing the need for it achievement).

1.2 Hypertension of pregnant women. Classification, risk control

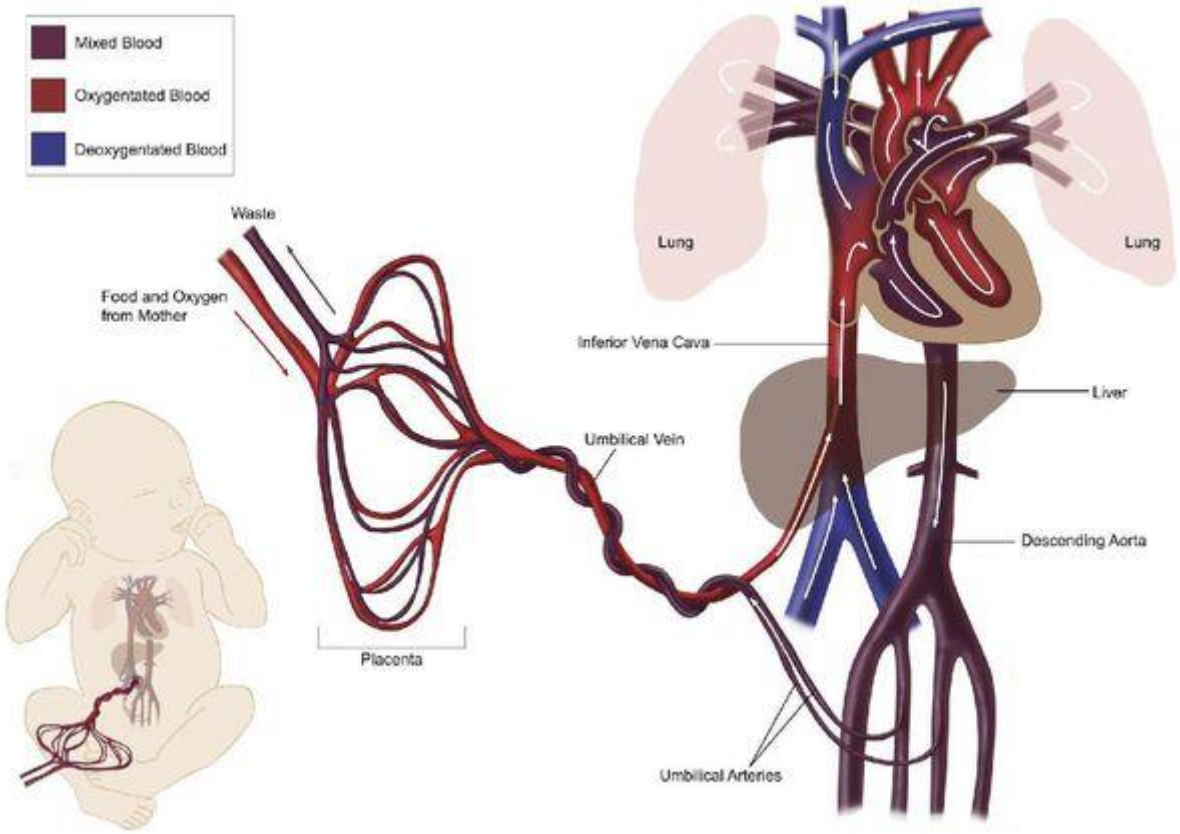
Normal blood pressure during pregnancy is considered to be the one that provides optimal blood supply to the placenta, and hence the fetus. The physiological course of pregnancy provides normal blood pressure at 20-24 weeks of gestation. In the first trimester of pregnancy, the level of progesterone increases, which helps to relax blood vessels and slightly reduce blood pressure. With increasing gestational age, blood pressure gradually increases, due to a significant increase in circulating blood volume, weight gain of 10-15 kg, sodium retention, increased cardiac output, plasma flow rate and hormone levels in the body. Hormonal activity of the placenta is due to hyperfusion of trophoblast cells and is a reflex mechanism aimed at increasing maternal circulation. The secretion of catecholamines by the placenta lasts for a certain period of time, which affects the blood pressure [52].

In the first hours after childbirth during the physiological course of the postpartum period, the pressure decreases, which is due to a decrease in the secretion of catecholamines in the body of the mother. According to the principle of negative feedback, the level of adrenaline and noradrenaline in the blood serum increases on the second day after childbirth, and on the 3rd-6th day after childbirth its maximum values are registered in women, with subsequent gradual normalization. Such dynamics is typical for both healthy women and women suffering from any form of hypertension [1, 29].

The risk of preeclampsia increases if in the second trimester of pregnancy the average blood pressure is above 90 mm Hg. In pregnant women with late toxicosis, the clinical course of the postpartum period and the biochemical processes of

recovery of catecholamine reserves are different than in the physiological course of pregnancy and childbirth. Restoration of blood catecholamines in pathological pregnancy occurs only on the 8th day, which indicates reduced adaptive capacity of the sympathoadrenal system in women with preeclampsia.

Pathological processes in hypertension during pregnancy are layered on the processes of adaptation of the cardiovascular system to the delivery and birth of a child. During pregnancy, another (third) circle of blood circulation is formed (Fig. 1.1.).



Picture 1.1 Blood circulation in pregnant women

Hypertension (AH) during pregnancy is registered in 8-10% of cases and significantly increases the likelihood of adverse events for both mother and fetus. Pregnancy hypertension is a heterogeneous concept that combines different clinical and pathogenetic forms of hypertensive conditions. But now among scientists there are no common criteria for definition, characteristics and even terminology. Thus, in many European countries, doctors use the term preeclampsia, in the United States and Britain - preeclampsia, in Japan - toxemia [8, 44].

Hypertensive disorders during pregnancy can be classified as follows [1, 7, 63]:

1. Chronic or present: high blood pressure (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥90 mm Hg in two measurements) before pregnancy or 20 weeks of pregnancy. Chronic hypertension complicates 1-5% of all pregnancies and usually persists for 6 months after delivery.
2. Gestational hypertension, including preeclampsia: hypertension develops after 20 weeks of pregnancy (usually after 37 weeks) and is registered for another 6-12 weeks after delivery; it occurs in 5-10% of pregnancies, most often in multiple. It is defined as gestational hypertension associated with significant proteinuria.
3. Primary preeclampsia: headache, epigastric pain, visual disturbances, convulsions.
4. Iatrogenic: due to the use of drugs: nonsteroidal anti-inflammatory drugs, horn derivatives to stop bleeding, ephedrine, drugs to correct hypovolemia, etc.
5. Pain (in case of inadequate analgesia).
6. Anxiety.

Chronic and gestational types of hypertension in pregnant women increase the risk of preeclampsia, eclampsia and other causes of maternal morbidity and mortality, including hypertensive encephalopathy, stroke, renal failure, left ventricular failure, HELLP syndrome (hemolysis, elevated liver enzymes) and

With hypertension, not only the level of serum catecholamines increases, but also the density of adrenergic innervation increases, which leads to local hypercatecholemia [27, 31].

Careful monitoring of blood pressure fluctuations throughout pregnancy provides an opportunity to understand and avoid all possible risks for both the woman and the fetus [26, 28].

The risk of fetal mortality or morbidity is increased due to decreased uteroplacental blood flow, which can lead to vasospasm, growth retardation, hypoxia and premature placental abruption. Results are worse if severe hypertension (systolic blood pressure ≥ 160, diastolic blood pressure ≥ 110 mm Hg, or both) or is

accompanied by renal insufficiency (eg, creatinine clearance <60 ml / min, serum creatinine> 2 dl [> 180 mol / l]).

Due to the constant high blood pressure and its uncontrollability by the woman and the doctor, the blood vessels lose their tone and their walls thicken. As a consequence of impaired blood supply to organs and tissues, which adversely affects their work and blood circulation in the placenta. Due to the fact that a person gets used to high blood pressure, it becomes clear that a pregnant woman pays attention to the problem only in the period of exacerbation, when blood pressure rises particularly high (for each individual), which negatively affects the whole body and fetus. Hypertension, however, is complicated by serious disorders of the internal organs, which can lead to disability or death of both mother and fetus.

The main complications of hypertension relate to the heart, brain, kidneys [36, 38]. In addition to such dangerous phenomena as heart attack or stroke, hypertension leads to angina, brain and lung edema. Any complication triggers a chain reaction, because it has its own complications that impair quality of life, lead to disability, disability and death [46, 70].

In the presence of complications of hypertension, symptoms from the affected target organs are noted:

- heart - heart rhythm disorders, heart pain, shortness of breath, edema;
- brain - deterioration of intellectual abilities, dizziness, neurological disorders;
- eyes - impaired vision, up to blindness;
- peripheral arteries, frostbite of the extremities, intermittent claudication;
- kidneys - nocturnal urination, edema.

In Figure 1.2. the risks of complications of hypertension are given.

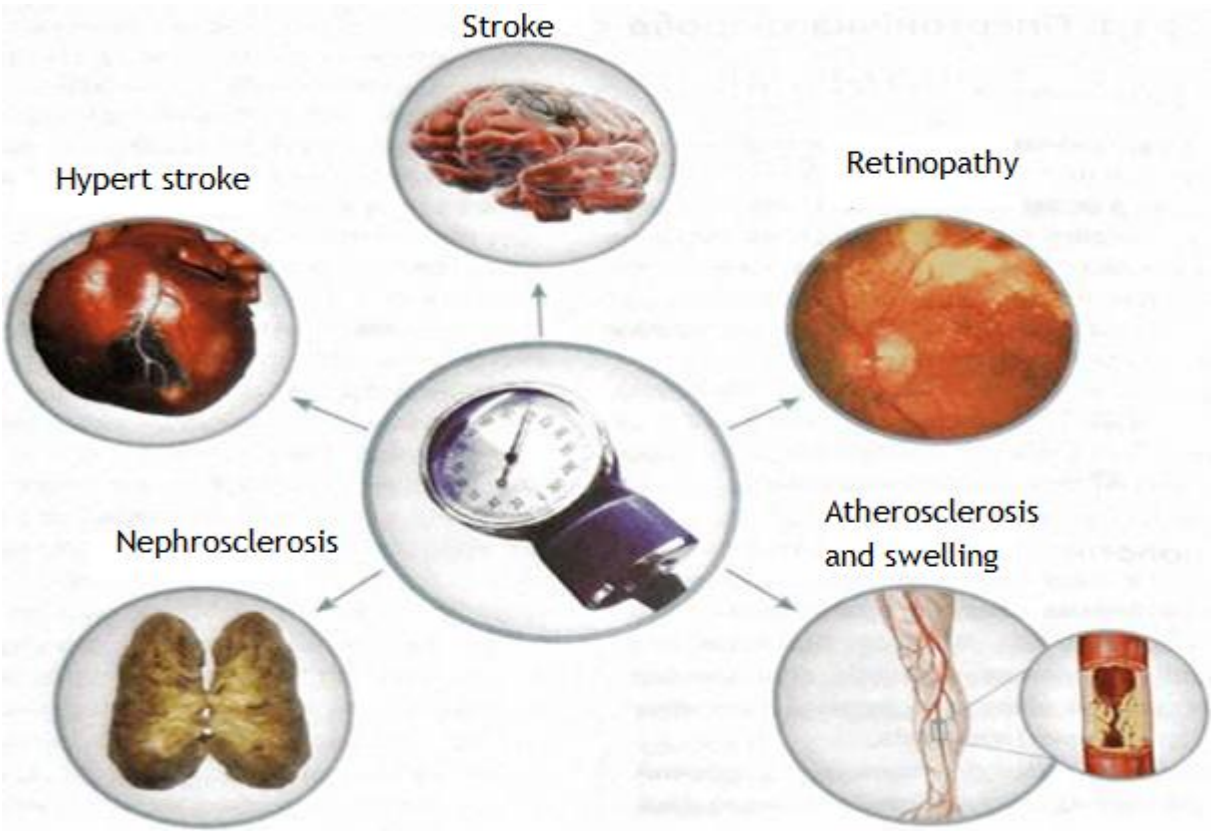


Figure 1.2 Complications of hypertension

For hypertension of pregnant women stages are determined by the studied level of blood pressure and depend on the presence of complications:

• Stage I - no complications;

• Stage II - the appearance of changes in one or more target organs (heart, blood vessels, brain, eyes, kidneys);

• Stage III - the presence of associated clinical conditions, ie gross organic pathology of target organs (heart attack, angina, stroke, renal failure, retinal hemorrhage, optic edema).

The most dangerous complications of pregnancy, childbirth and early postpartum period in women with hypertension [1, 7]:

• placental insufficiency;

• fetal growth retardation syndrome;

• fetal death;

• death of a child in the early postpartum period;

• premature detachment of the normally located placenta;
• obstetric bleeding;
• eclampsia;
• severe life-threatening blood clotting disorders;
• acute renal damage;
• pulmonary edema;
• hemorrhage and retinal detachment;
• stroke.

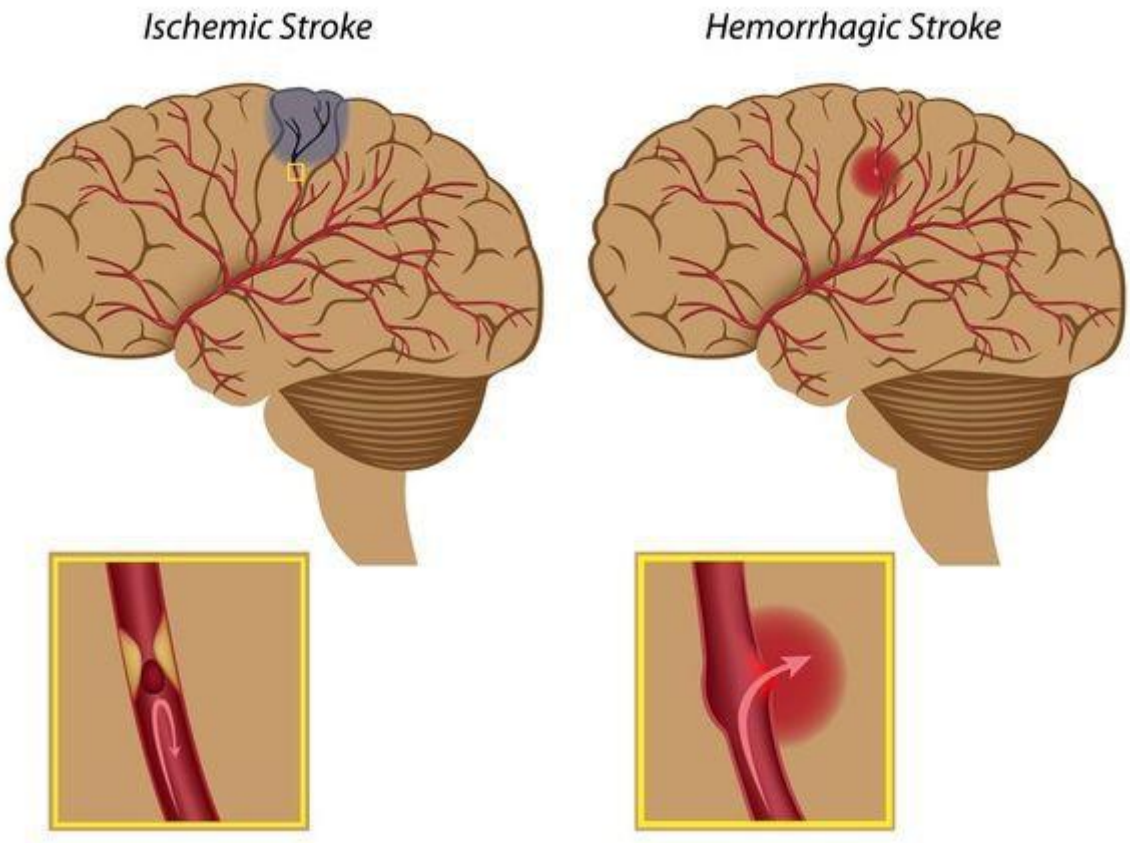


Figure 1.3 Complications of hypertension, effects on cerebral vessels

Women with severe hypertension are at high risk of life-threatening complications, so despite the lack of evidence-based recommendations, pregnant women are still prescribed antihypertensive therapy [35, 41, 42, 54].

1.3 Diagnosis and classification of hypertensive disorders during pregnancy

The analysis of maternal deaths from severe hypertension shows that, despite sufficient study of this problem, in many cases women die from organizational and professional errors of medical staff not only obstetrics and gynecology, but also ambulances and emergency services.

During pregnancy, the diagnostic process solves the following tasks:

- determining the degree of hypertension;
- determination of the condition of target organs;
- determining the risk of preeclampsia;
- determining the effectiveness of treatment.

Blood pressure has physiological fluctuations during the day. Blood pressure usually decreases at night in women with mild preeclampsia and chronic hypertension, but in severe preeclampsia, blood pressure has distorted fluctuations with a peak of blood pressure at 2 o'clock at night. The procedure of diagnosis, measurement of blood pressure is of great importance to prevent the development of premature complications [46,59].

Diagnosis of hypertension is difficult, both outside of pregnancy and throughout pregnancy, when it is not possible to use most diagnostic manipulations (invasive, radiological, isotopic). Therefore, the peculiarities of the anamnesis and diagnostic tests performed before pregnancy are of great importance. Management of all term of pregnancy demands from the gynecologist qualitative assessment of all laboratory and instrumental researches.

Laboratory and instrumental studies during pregnancy:

A. To all pregnant women:

a) detailed blood test (for hemoglobin, erythrocytes, leukocytes, ESR);
b) analysis of urine for the presence of protein;
c) analysis of urine for the presence of erythrocytes, leukocytes;
d) analysis of urine for sugar;

e) serum potassium;

f) serum creatine or urea nitrogen;

g) electrocardiogram;

h) fundus examination;

i) manual examination of the thyroid gland.

B. Depending on the results of history and examination:

a) blood sugar;

b) cholesterol and blood triglycerides;

c) calcium, phosphorus, serum uric acid;

d) echocardiogram;

e) ultrasound of the kidneys;

f) urine culture;

g) urine analysis for catecholamines.

Examination of women with hypertension when planning a pregnancy or deciding whether to preserve the pregnancy should include examination of target organs, as their risk increases for both mother and fetus increases. Careful monitoring of a woman's condition in the second half of pregnancy is especially important for timely diagnosis and treatment of preeclampsia. Pregnant women with hypertension should be registered with a physician, gynecologist and endocrinologist.

Primary hospitalization of pregnant women at risk occurs up to 12 weeks in order to address the issue of further preservation of pregnancy. The last hospitalization takes place 2-3 weeks before delivery in order to choose the method.

Pressure measurements are performed according to standard procedures, it is recommended to perform on both arms, but in the subsequent measurement mainly on the arm with a higher blood pressure, mostly sitting or lying on the left side. If aortic dissection is suspected, blood pressure is also measured in the lower extremities.

According to both European and American recommendations, the diagnosis and control of hypertension are used not only office (clinical, physician-measured) blood pressure measurements, but also outpatient, which are given (in Table 1.3).

Table 1.3
Hypertension criteria based on clinical (office) blood pressure measurement [46, 59]

Measurement	**CBP/DBP, mm Hg.**
Office BP (clinical)	≥ 140 and / or ≥ 90
Outpatient BP measurement	
Average BP within 24 hours	≥ 130 and / or ≥ 80
Average daily BP (during the waking period)	≥ 135 and / or ≥ 85
Average BP (during sleep)	≥ 120 and / or ≥ 70
Home measurement	≥ 135 and / or ≥ 85

According to the European Society of Hypertension (ESH), the European Society of Cardiology (ESC) and the European Society of Atherosclerosis (ESA), more than half of pregnant women, especially in the second trimester diagnosed with hypertension, have an additional risk factor - overweight and obesity (45%), elevated levels of low-density lipoprotein, cholesterol and triglycerides (25%), hyperglycemia (15% -20%), hyperuricemia (18%) and metabolic syndrome (38%) [73].

In the case of their simultaneous presence, elevated blood pressure and other risk factors may exacerbate each other, which leads to an increase in the overall risk of CVD, which exceeds the sum of its individual components [17, 73, 74].

Management of the first trimester of pregnancy requires a doctor to qualitatively assess all risk factors, regular monitoring of blood pressure, determination of the placental index of the uterine artery, PIGF and, if necessary, prophylactic acetylsalicylic acid for 11-14 + 6 days until the 36th week of pregnancy.

When diagnosed with calcium deficiency in the diet (<800 mg / day), it is also recommended to prescribe calcium supplements in terms of elemental calcium 1.5-2 g / day.

If the patient has all the prerequisites for complications and they are already formed, help is possible only by detecting early signs of critical lesions of target organs in pregnant women, namely glomerular apparatus - proteinuria, vascular - increased blood pressure, aspartate aminotransferase, alanine aminotransferase, alkaline, alkaline, alkaline hemolysis - liver damage (International Journal of Obstetrics & Gynecology, 2019).

Improving the prognosis of hypertension in pregnant women is possible through the appointment of multivitamins, trace elements, including vitamin D and calcium [62]. Clinical studies by Chinese doctors have shown that prescribing multivitamins halves the incidence of preeclampsia in early pregnancy. It is proved that a deficiency of arginine, folic acid to reduce the level of homocysteine, create all the conditions for the irreversible process of preeclampsia (Fig. 1.4).

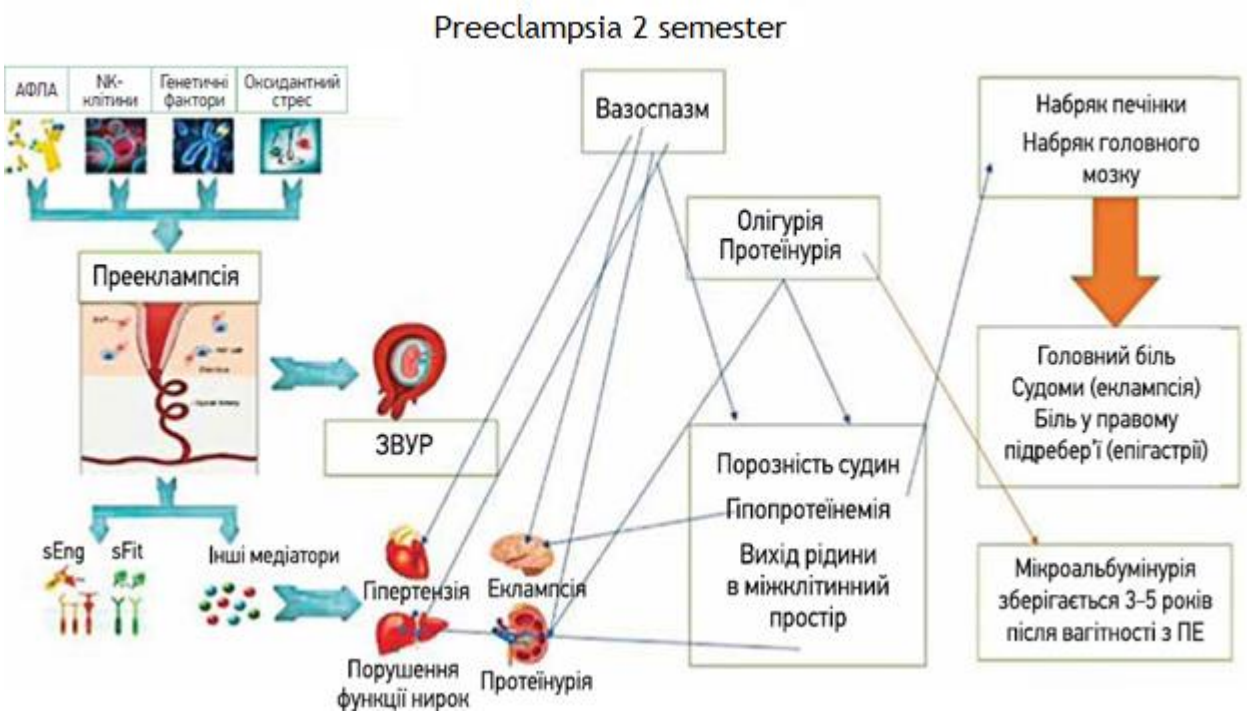


Figure 1.4 - Pathogenesis of hypertension in preeclampsia of the second trimester under conditions of deficiency in pregnant women [1]

1.4 Laboratory indicators

When considering various conditions and diseases, the basic indicators according to which it is possible to observe dynamics are important. In table 1.4. this section shows the norms of laboratory parameters for women.

Table 1.4.

Norms of laboratory parameters in women [7, 46]

Indicator	**N**ormal
Creatinine	44-97 μmol / l
Urea	1.92-4.51 mmol / l.

ALT	up to 32 un / l
AST	up to 31 un / l
Uric acid	150-350 μmol / l.

Creatinine is a metabolite of creatine phosphate, the final dehydrated product of creatine metabolism. This is an indicator of metabolic disorders, a by-product of metabolic processes in muscles. Determination of creatinine allows to assess glomerular filtration, as it is released only by glomeruli, not reabsorbed in the renal tubules [62, 69].

Deviation from the norm:

Increased level signals: renal failure, muscle damage, exercise, excessive meat consumption.

Reduced level is observed in: decreased muscle mass, pregnancy, protein deficiency, li ver disease [68, 71].

Urea is the end product of the breakdown of proteins in the body, which is formed in the liver as a result of a cascade of complex biochemical reactions. The purpose of this process is the excretion of a number of nitrogenous substances (metabolites that can harm it). One such metabolite is ammonia. In itself, it is quite aggressive to many organs and tissues, especially the brain.

The result of an analysis that results in elevated urea (azotemia) may indicate the presence of [68]:

- Kidney disease (pyelonephritis, glomerulonephritis, acute or chronic renal failure, renal tuberculosis);
- Urolithiasis (complications of urine outflow);
- Heart or liver failure (acute or chronic);
- Malignant processes;
- Bleeding of any origin (including internal - from the gastrointestinal tract or others);
- Intestinal obstruction;

- Burn disease, shock, intoxication, etc.

- Exercise;

- Drugs (glucocorticoids, androgens).

Urea, the result of which is below normal may be associated with diseases such as hepatitis, cirrhosis, hepatic coma, and a moderate decrease in children during the phases of active growth, phosphorus or arsenic poisoning.

It is known that a decrease in urea levels below normal is observed during pregnancy.

It is also known that the analysis of urea will show its low content if a person eats mostly plant foods, as well as vice versa: people whose diet contains a large amount of protein (meat, eggs, fish, dairy products) - will have high urea levels.

AST, ALT - an enzyme involved in energy production in such a process as the Krebs cycle by transferring amino groups. Contained in the mitochondria and cytoplasm of the liver, erythrocytes, heart, kidneys, skeletal muscle and pancreas. The activity of the enzyme is equal to the degree of tissue damage. The largest amount of enzyme is localized in the heart.

Increased ACT activity may be due to viral hepatitis, muscle injuries, liver damage, myocardial infarction, liver cirrhosis, chronic hepatitis, and others.

ALT is a transaminase enzyme involved in the transfer of amino groups. The largest number is localized in liver cells. In general, transferases indicate myocardial damage, infectious diseases, jaundice, liver disease [32, 66].

Uric acid is the end product of the metabolism of purine acids, which are contained in the DNA and RNA of all cells in the body. Purines enter the bloodstream due to cell death (up to 80%) or in the form of food (red meat, liver, fish, legumes, beer, wine). In the liver under the influence of xanthine oxidase is the synthesis of uric acid, 70% of which is excreted by the kidneys.

Increased production of uric acid or impaired excretion due to decreased renal function leads to hyperuricemia, which is manifested by kidney stones and gout. Elevated uric acid causes a condition such as hyperuricemia (> 420 mmol / l), which is an additional risk factor for hypertension.

Photo and figure 1.5 show developed for the diagnosis of measures to control changes in the functional activity of the kidneys and metabolic processes in the body in various types of pathology.

Photo. The use of test strips allows you to quickly (in 1-2 minutes) to analyze from 5 to 13 urine parameters.

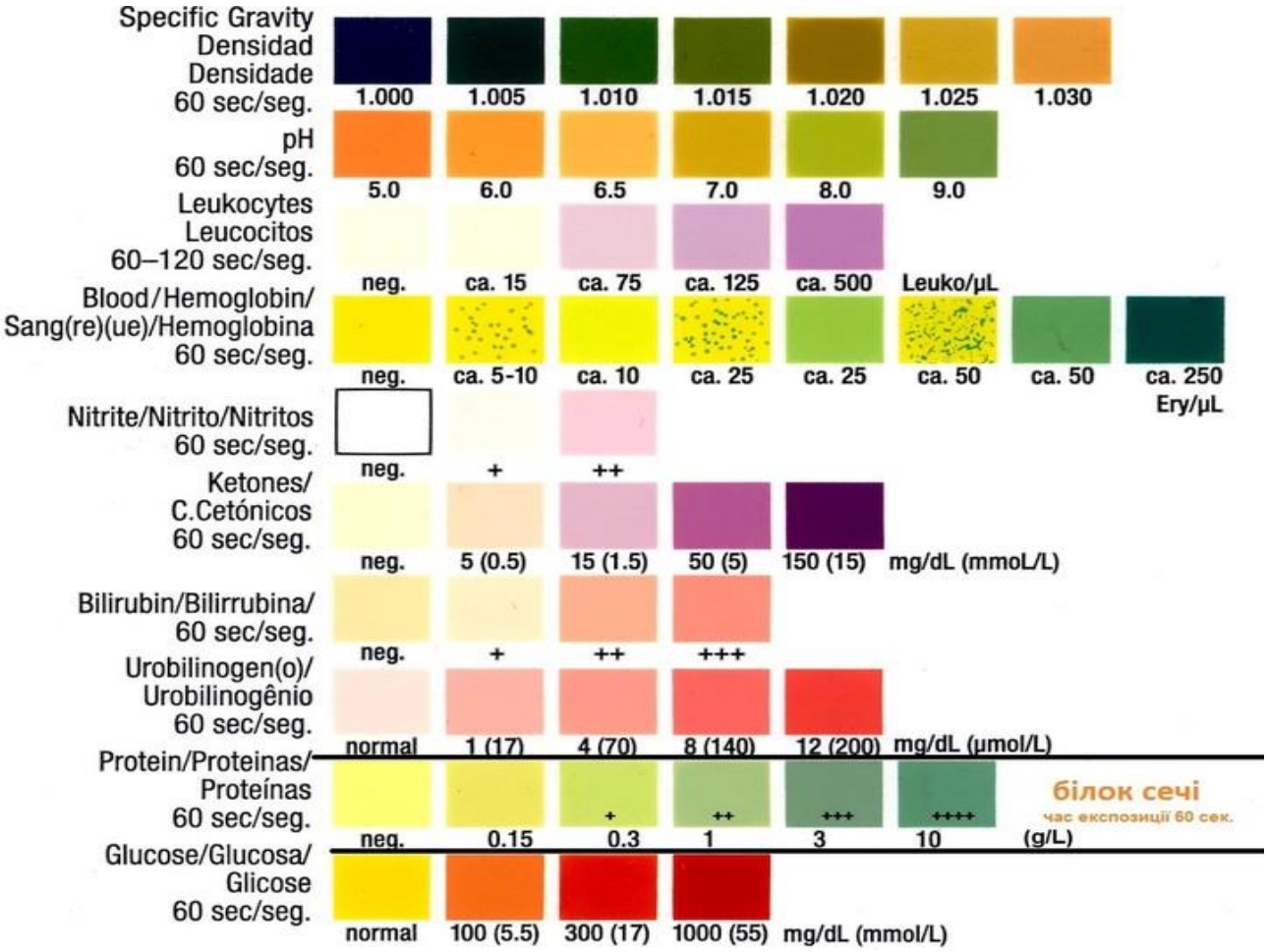


Figure 1.6 Proteinuria test strip is determined in 60 seconds.
The concentration of protein in the urine of 0.3 g / l English-speaking doctors designate as "+", 1 g / l - "++", 3.0 g / l - "+++".

Foreign authors attribute edema to a phenomenon that does not affect the prognosis of pregnancy, perinatal morbidity and mortality, if the mother does not develop hypertension, proteinuria.

1.5 Drug therapy of hypertensive disorders during pregnancy

Drug pharmacotherapy of pregnant women involves general agreement on common issues, which comes to the obstetrician-gynecologist together with the therapist, as well as, if necessary, with other specialists - cardiologist, endocrinologist, neurologist.

Pharmacotherapy of symptomatic hypertension is almost no different from that of hypertension [62, 64, 65]. However, the effect of therapy is often less pronounced. Thus, the correction of stable hypertension caused by renal artery stenosis is performed with surgical manipulations. Hypertension of endocrine origin requires treatment of the underlying disease.

Treatment of mild or moderate hypertension without renal failure during pregnancy is debatable. The problematic questions are: does treatment improve the outcome of pregnancy and to what extent the risks of drug therapy outweigh the risks of untreated disease [48, 61]. It should be borne in mind that uteroplacental blood flow cannot regulate itself, lowering maternal blood pressure can dramatically reduce it.

It is known that drug therapy during pregnancy is often contraindicated due to the high risk of teratogenic effects [62, 75]. The placental barrier is overcome by a large number of drugs. If the patient's condition allows, doctors try to use non-drug therapy, i.e., lifestyle modification, namely - increase sleep duration, stress management, meditation, diet, walking in the air, general strengthening exercises.

The unpredictable nature of complications in severe hypertension in pregnant women requires hospitalization and close monitoring in specialized centers that have sufficient resources for intensive care of the mother and newborn.

In case of moderate or severe hypertension, treatment includes antihypertensive therapy, careful monitoring, and in case of worsening of the condition - termination of pregnancy or childbirth, depending on gestational age. Induction of labor is recommended after the 37th week of pregnancy. Up to 10% of mortality in pregnant women occurs in the postpartum period. Other possible complications of severe postpartum hypertension are caused by stroke or eclampsia. There are currently no randomized clinical trials, and in many parts of the world most recommendations are based on expert consensus.

The goals of treatment of hypertension in pregnant women are:

- prevention of complications associated with high blood pressure;
- preservation of pregnancy;
- normal fetal development and timely delivery.

There are two ways to treat hypertension during pregnancy:

- outpatient;
- stationary - required for:
- gestational hypertension (blood pressure ≥ 140/90 for ≥ 20 weeks of pregnancy);
- hypertensive crisis (rapid increase in blood pressure ≥ 170/110);
- preeclampsia (blood pressure ≥ 140/90 + protein in the urine);
- eclampsia (convulsions).

Types of outpatient treatment:

- non-medication - normalization of lifestyle and nutrition;
- medication - taking drugs under medical supervision and blood pressure control [46, 59].

In mild hypertension, traditional therapy is used, followed by the appointment of antihypertensive drugs if necessary [1, 62].

ESC experts on the study of hypertension in pregnant women for the appointment of antihypertensive therapy determine the level of systolic blood pressure not less than 150 mm Hg, and diastolic - not less than 100 mm Hg, or the presence of clinically defined target organs - hypertrophy left ventricle, renal failure.

According to other guidelines, it is recommended to start therapy with blood pressure greater than 170/110 mm Hg. [46]

The most common antihypertensive drugs for the treatment of hypertension in pregnant women are shown in table 1.5.

Drugs of choice for antihypertensive therapy during pregnancy are:

1. agonist of alpha2-adrenoceptors - methyldopa;

2. beta-adrenoceptor blockers - atenolol;

3. non-selective blocker of alpha and beta-adrenoceptors - labetalol;

4. dihydropyridine calcium channel blockers - nifedipine, felodipine, izradipine;

5. magnesium sulfate; apressin; renin inhibitors

It is recommended to start therapy with alpha2-adrenoceptor agonist - methyldopa, beta-blockers or calcium channel blockers.

The use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) and aldosterone antagonists should be avoided.

Angiotensin-converting enzyme inhibitors (enalapril, lisinopril, captopril, ramipril) are not recommended during pregnancy and several weeks after delivery, as there is a hypothetical risk of cardiovascular and renal side effects due to lack of scientific experience. this issue. It is known that ACE inhibitors can cause fetal growth retardation, bone dysplasia with impaired skull ossification, shortening of limbs and even fetal death. In the case of ACE inhibitors, treatment is continued until the appearance of any side effects in the fetus under the conditions of weekly ultrasound monitoring or other studies [61, 62].

Table 1.5 Recommended antihypertensive therapy

Nitroglycerin	Short-acting nifedipine	Hydralazine	Labetalol	**1**	**Drug**
Direct vasodilator	Dihydropyridine calcium channel	Direct vasodilator	α1-Nonselective β-adrenoceptor blocker	**2**	**Mechanism of action**
Orally	In / v bolus	Intravenous infusion	In / v bolus	**3**	**Method of administration**
1–5	5–10	10	5–10	**4**	**Beginning of action,**
0,05	2–4	12	2–6	**5**	**Duration of action,**
10–20 mg	5 mg intravenousl	1-2 mg	10–20 mg	**6**	**Initial dose**
If necessary, repeat after 30 minutes	5–10 mg IV every 20–40 min	Increase by 1 mg every 10 minutes	20–80 m, every 20–30 min.	**7**	**Dose titration**
200 mcg / min	30 mg	30 mg	300 mg	**8**	**The maximum dose**
	Fetal distress	Fetal distress, cesarean section, Apgar score <7,	Fetal distress, neonatal bradycardia, hypoglycemia	**9**	**Perinatal problems**
			AV-blockade of the II- or III-degree. CH.	**10**	**Contraindication**
Headache, reflex tachycardia	Uncontrolled hypotension, stroke	Headache, palpitations, tachycardia, nausea / vomiting,	Bronchospasm (caution should be exercised when prescribing to women with	**11**	**Side effects**

Continuation of the table. 1.5

1	Esmolol	Nicardipine	Urapidil	Sodium nitroprusside
2	B1-adrenoceptor blocker	CCB	B1-adrenoceptor	Non-selective direct nitric oxide inhibitor
3	Intravenous infusion	Intravenous infusion	Intravenous	Intravenous infusion
4	<1	1–5	3–5	<1
5	0,25-0,50	4–6 h	4–6 h	2–3 min
6	50 mcg/kg/min	5 mg/h	5–40 mg/h	0,25 μg / kg / min
7	Increase by 50 μg / kg / min every 4 minutes	Increase by 2.5 mg / h every 5–15 minutes		Increase by 0.25-0.5 μg / kg / min every 2-3 minutes
8	300 mcg/kg/min	15 mg/h	40 mg/h	5 μg / kg / min
9	Fetal bradycardia			Toxicity of cyanide and thiocyanate to
10	AV-blockade of the II- or III-degree, heart	Hepatic failure		
11	First-degree heart block, bradycardia in women, bronchospasm	Tachycardia, hot flashes, headache		Nausea, vomiting

Angiotensin receptor antagonists are contraindicated throughout pregnancy and breastfeeding, as they are teratogenic, and imidazoline receptor agonists are still poorly understood [52, 64, 65].

The drug alpha2-adrenomimetic - methyldopa is preferred by a large number of clinicians on the basis of reports of stable uteroplacental circulation during long-term follow-up. The drug has no long-term risks of adverse side effects in later life in both women and children [1, 46, 59].

Usually, therapy is started with methyldopa, beta-blockers or calcium channel blockers. Labetalol intravenously and nifedipine orally are first-line drugs for the treatment of hypertension during pregnancy. It is not recommended to use methyldopa in case of urgent blood pressure lowering.

To reduce circulating blood volume (CBV) and peripheral edema, taking into account all possible risks, your doctor may recommend diuretics. Diuretics, by reducing maternal CBV, consistently and persistently can lead to the risk of fetal growth retardation. Diuretics are sometimes prescribed to pregnant women at a later date. The diuretic is selected taking into account the individual characteristics of the patient, depending on the causes of ill health and the need for intensity of the effect.

Pregnant women with hypertension are prescribed diuretics based on the following components [48, 59]:

• goldenrod;
• lovage;
• horsetail;
• artichoke;
• goldsmith

Furosemide can be prescribed only in the second trimester of pregnancy,7 hydrochlorothiazide in the second half of pregnancy, theobromine increases the risk of fetal tachycardia, so it is prohibited for the entire pregnancy, xipamide - increases blood clotting and is also contraindicated in pregnant women.

Intravenous magnesium sulfate is recommended for the prevention of eclampsia and seizures in pregnant women. Magnesium sulfate is not combined with calcium channel blockers due to the high risk of synergism.

Current guidelines for the management of pregnant women with chronic and gestational hypertension are the same and depend on the severity of the pregnancy [46]. It is known that chronic hypertension can be more severe, and in gestational hypertension the increase in blood pressure often occurs only in late pregnancy and does not require treatment. However, if any preventive measures do not lead to the

stabilization of normal blood pressure, many experts recommend the use of drug therapy.

The study of pathogenetic mechanisms of the development of hypertensive syndrome in pregnant women allowed to develop the principle of combination drug therapy. The combined use of magnesium drugs, adrenergic drugs - clonidine or methyldopa and calcium channel blockers in pregnant women at risk for severe preeclampsia allows you to prolong the pregnancy to the required time. Abortion is recommended in the absence of treatment and occurs in less than 7.7% of cases. Perinatal mortality is 2.2%. Carrying out preventive treatment in pregnant women with hypertension and autonomic dysfunction of the hypertensive type with clonidine and verapamil, starting from 20-24 weeks, has a stable hypotensive, diuretic and sedative effect in 92.5% of patients.

The purpose of pharmacotherapy of a patient with hypertension is to achieve the maximum reduction of the total risk of cardiovascular complications by achieving and maintaining the target blood pressure level less than 120/80 mm Hg. (in patients with diabetes mellitus, in chronic kidney disease, the target blood pressure is 130/80 mm Hg), modification of risk factors, effective treatment of concomitant clinical conditions.

Medical treatment of concomitant diseases (coronary heart disease, diabetes, etc.) is carried out in accordance with current medical and technological documents.

Prevention of preeclampsia in pregnant women with chronic hypertension is as follows [1, 46, 62]:

1. Acetylsalicylic acid 60-100 mg / day, starting from 20 weeks of pregnancy;
2. Calcium supplements 2 g / day, starting from 16 weeks of pregnancy;
3. Inclusion in the diet of seafood with a high content of polyunsaturated fatty acids;
4. Do not limit the use of salt and liquid.

If the target blood pressure is not reached, it is necessary to make sure that the patient follows the recommendations for taking drugs, to correct the therapy.

In case of ineffectiveness of drug therapy (provided that the drugs are prescribed in adequate doses) - referral to health care facilities that provide secondary care, the ability to monitor the patient's condition. If it is impossible to monitor and / or develop a complicated hypertensive crisis, the patient is referred to secondary inpatient care as soon as possible.

Desirable actions: in case of ineffectiveness of drug therapy to perform outpatient blood pressure monitoring or blood pressure monitoring at home

Recommendations for the management of pregnant women with chronic and gestational hypertension are the same and depend on the severity. However, chronic hypertension can be more severe. In gestational hypertension, the increase in blood pressure often occurs only in late pregnancy and does not require treatment.

SECTION 2 MATERIALS AND METHODS OF RESEARCH

In our work we used methods for analysis and data obtained from the monitoring of medical histories of pregnant women with a history of hypertension and other concomitant pathological conditions that did not directly affect the purity of the data. The methods used for the study were standard or partially modified according to the specifics of the topic under consideration in our work and the specifics of the research group of patients.

2.1 Clinical characteristics of patients with hypertension

The study analyzed 730 case histories of pregnant women diagnosed with hypertension (AH) and selected 50 case histories for detailed analysis.

The mean age of patients was 27.7 ± 9.7 years, among them were 203 (27.8%) women aged 33.1 ± 2.2 years. According to statistics, in Europe women give birth for the first time at the age of 28 ± 3 years, and in Ukraine - 25 ± 3. A normal physiological

pregnancy and the birth of a healthy child is possible in 85%, but it is important to be aware of what problems may arise and take the necessary measures.

According to the received analytical studies from all registered cases of pregnancy in 2021 complicated by edema, proteinuria and hypertensive disorders is 6.4 per 100 pregnancies, including cases of preeclampsia is 2.13 per 100 pregnancies, of which 11.9% are severe forms of preeclampsia and eclampsia, which is 0.25 per 100 pregnancies.

In most cases, high blood pressure, proteinuria and edema (preeclampsia) disappear in the days following childbirth or abortion. Women who have had pregnancy-related hypertension are at risk for developing hypertension later in life.

2.2 Materials and methods of research

Modern scientific developments in the monitoring, prevention and medical treatment of pregnant women with hypertension indicate that in the first place the doctor takes into account all the degrees of risk of adverse termination of pregnancy for mother and child. Up to 12 weeks, the issues of preservation, i.e., the possibility of pregnancy are resolved. In the case of pregnancy, it is important to constantly highly qualified observation in a specialized medical institution.

The following indicators were studied in the analyzed case histories: blood pressure, ultrasound of the uterus, kidneys and other abdominal organs, electrocardiography and echocardiography, creatinine, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), creatine, urinary acid and urea. The most common concomitant pathologies in hypertension in pregnant women at different times have been identified.

Combinations in the pharmacotherapy of hypertension and means of lifestyle modification of patients are analyzed.

2.3 Determination of average values in the experiment

During the study of samples and predictions of the experiment, calculations were performed, the data of which are given in this paper in the tables. Most often, the data obtained in studies were processed by mathematical statistics. First of all, the calculations were performed to obtain average mathematical values according to the standard formula 2.1.

$$\bar{a} = \frac{a_1 + a_2 + ... + a_n}{n} \qquad 2.1$$

$\bar{a}$ - average mathematical value;

a_1, a_2 i a_n - processed values;

n - the number of sample values.

If necessary, graphs and charts were built based on the calculated data.

SECTION 3 RESULTS OF OWN RESEARCH

The results of research on the case histories of women with arterial hypertension at different stages of pregnancy, different age categories, were the results presented in this section of our work.

3.1 Analysis of the risks of hypertension in pregnant women

Despite the large number of antihypertensive drugs to date, effective pharmacotherapy of hypertension in pregnant women remains an urgent problem. The current clinical practice of the obstetrician-gynecologist proves that in pregnant women, especially in the second trimester, a combination of several somatic pathologies is quite common. Most often, hypertension in pregnant women is accompanied by such comorbidities as hepatic steatosis. chronic cholecystitis, chronic pancreatitis, nephrolithiasis, cardiosclerosis, etc. The question of the choice of rational pharmacotherapy in patients with comorbidity on the background of existing vascular pathology is acute. The combination of arterial hypertension, chronic kidney disease, liver steatosis, hepatitis and other pathologies in one patient forces us to emphasize the peculiarities of the management of such patients throughout pregnancy and for a long time in the postpartum period. The study provides an analysis of medical records of patients with comorbid pathologies, recommendations for the management of pregnant women with similar comorbid conditions. The presence of comorbid pathology in pregnant women requires more attention to the prescribed drugs with possible effects on the fetus, combinations should show minimal interaction, metabolic neutrality, positive effects on the damaged organ, which together will promote more effective treatment and minimize the risk of adverse reactions.

We analyzed laboratory parameters of biochemical analysis of blood in patients with hypertension. The data of the analysis are given in table 3.1 of this work.

Table 3.1.

Analysis of laboratory parameters in patients with hypertension

Indicator	**Average value**	**Laboratory reference values**
Creatinine, μmol / l	98,1±22,3	61-117
Urea, mmol / l	6,7±4,2	2,5-8,3
AST, U / L	34,1±8,2	0-41
ALT, U / L	36,5±12,4	0-40
Uric acid, μmol / l	364,7±102,1	200-420/140-340

Thus, patients with hypertension had an average creatinine level of 98.1 ± 22.3 μmol / l, an average urea level of 6.7 ± 4.2 mmol / l and an average uric acid level of 364.7 ± 102.1 μmol / l. The average level of ALT and AST was 34.1 ± 8.2 U / L and 36.5 ± 12.4 U / L, respectively.

The number of patients with hypertension who had certain indicators higher than the reference values was analyzed (Fig. 3.1).

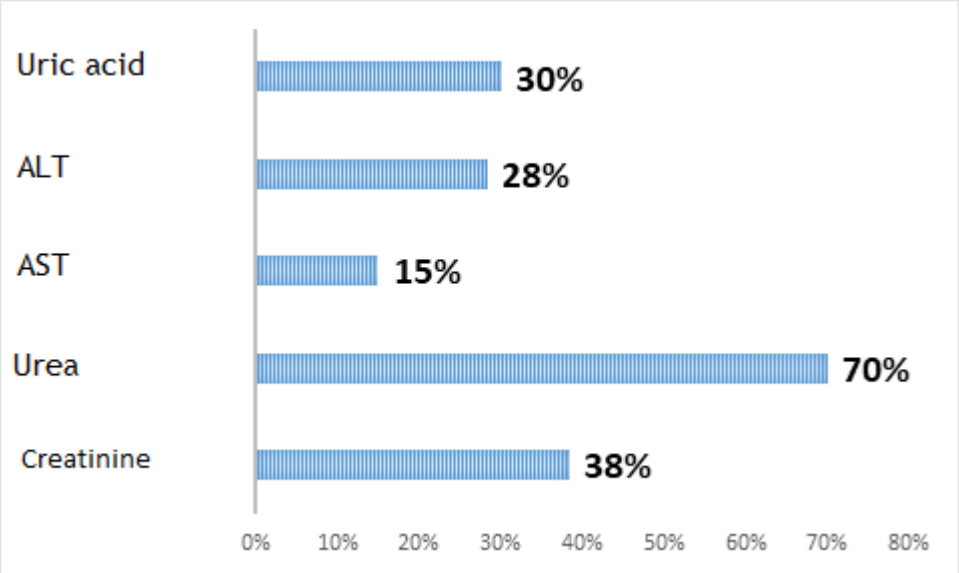


Figure 3.1 - Frequency of exceeding the reference values of laboratory indicators of renal and hepatic function in pregnant women with hypertension.

In addition, an increase in creatinine levels was found in 38% of patients with hypertension, an increase in urea levels in 70% of pregnant women and a high level of uric acid in 30% of those examined.

Elevated transaminases were found in 15% of pregnant women with hypertension (AST) and 28% of patients with hypertension (ALT).

3.2 Risks of pregnant women with concomitant pathology of the urinary, hepatobiliary system and pathologies of the gastrointestinal tract

The use of statins is a long-term therapy, and during pregnancy and breastfeeding their appointment is possible only when the pregnant woman is well informed about the possible risks to the fetus. The teratogenic properties of statins are still poorly understood, but they remain contraindicated for pregnant women worldwide.

Among patients with hepatic steatosis, more than half (54%) have elevated transaminases, and patients with biliary tract disease have elevated transaminases and / or hyperbilirubinemia. Liver disease can alter drug kinetics. In hepatic insufficiency there is a decrease in the rate of metabolism of drugs that are biotransformed in the liver.

Drugs from the group of calcium channel blockers in pregnant women with impaired metabolic function of the liver there is a need for dose adjustment, as their metabolism occurs with the help of liver enzymes. From the group of ß-blockers (BB) it is necessary to pay attention to propranolol - a drug that undergoes intensive presystemic metabolism, there is an increase in systemic bioavailability in patients with liver disease, which is associated with decreased metabolic activity of liver enzymes. Therefore, the dose should be adjusted (reduce the dose of the drug).

Increased creatinine levels in pregnant women with hypertension indicate impaired renal filtration, renal failure. In renal failure, disorders in the

pharmacokinetics of drugs are manifested in increased blood concentrations of the drug, slow elimination of blood and decreased urinary excretion by the kidneys.

As a result, drugs prescribed for chronic renal failure should be used in smaller doses. The Cochrane Research Database indicates a similar nephroprotective effect of ACE inhibitors and ARBs. There is a need to reduce the dose of antihypertensive drugs. The nephroprotective effect of ACE inhibitors and ARBs has been proven and these groups of drugs are recommended for patients with renal disease [36]. The group of drugs - ACE inhibitors is contraindicated in pregnant and lactating women.

According to the ability to dissolve in water and fats, beta-blockers are divided into lipophilic and hydrophilic. The group of lipophilic beta-blockers includes metoprolol, betaxolol, propranolol, oxprenolol, pindolol, labetalol, they are mainly absorbed from the digestive tract, and the group of hydrophilic drugs such as sotalol, atenolol, nadolol. Drugs from the group of hydrophilic beta-blockers are unevenly and not completely absorbed from the digestive system, and excreted from the body by the kidneys and urine. Renal function is taken into account when prescribing hydrophilic beta-blockers, and the dose is reduced in patients with low GFR (less than 30–50 ml / min).

Amphiphilic BBs are soluble in fats and water (bisoprolol, celiprolol). Metabolism of lipophilic BB occurs mainly in the liver, which should be considered in pharmacotherapy of patients with liver disease, as well as in combination therapy with drugs inhibitors of microsomal liver enzymes.

Bisoprolol is an amphiphilic drug from the group of beta-blockers, scientific sources report greater safety in pharmacotherapy in patients with hypertension with concomitant liver and kidney disease, and studies indicate a low likelihood of interaction with drugs inhibitors of microsomal enzymes such as chlorine. , rifampicin and others. [37].

No dose adjustment is required during the treatment of patients with renal disease with CCB and ARBs as excretion occurs mainly by the liver.

For effective and safe therapy it is necessary to minimize the accumulation of active and potentially toxic metabolites in pregnant women with impaired renal and hepatic function.

3.3 Drug pharmacotherapy of arterial hypertension in pregnant women, combinations and possible interactions

It is known that none of the existing antihypertensive drugs is completely safe for the embryo and fetus. Given this, antihypertensive therapy in the first trimester of pregnancy (up to 13 weeks) is not recommended in any country in the world. Exceptions are patients with grade 3 hypertension and women who do not tolerate any increase in blood pressure. In the later stages of pregnancy, women with blood pressure 140/90-149/94 mm Hg. mostly also do not require treatment with antihypertensive drugs. Antihypertensive therapy is carried out when raising blood pressure to 150/95 mm Hg. and more. Prescribe the safest drugs for mother and fetus.

The frequency of administration of different groups of antihypertensive drugs was analyzed (Table 3.2).

Table 3.2

Antihypertensive drugs used in the pharmacotherapy of patients with hypertension

Group of drugs	Number of patients	%
ACE inhibitors	45	70
CCB	5	8,33
ARB	1	1,67
BB	27	45
Diuretics	41	68,33

After analyzing the pharmacotherapy of patients, we can conclude that such groups of drugs (Table 3.3) as ACE inhibitors (70% of appointments) and diuretics (68.3% of appointments) are drugs of choice for treatment, especially often prescribe drugs from these groups together or in the combined drug. In second place, BB, which

was prescribed in 45% of cases, CCB was prescribed to 8.3% of patients and ARB was prescribed in 1.7% of cases. According to the literature, the combination of ACE inhibitors or ARBs and diuretics has an economic advantage in terms of cost / effectiveness and is recommended for patients to optimize pharmacotherapy [47]. Such effectiveness of treatment in ordinary patients does not prove their rationality of appointment during pregnancy and breastfeeding women.

Consider possible methods of pharmacotherapy of pregnant women with hypertension.

According to recent studies, magnesium, ascorbic and folic acid, vitamin E, fish oil and garlic extract have no evidence of prevention of hypertension in pregnant women [48, 53]. Pregnant women with hypertension are advised to limit salt in the diet in accordance with existing recommendations.

Acetylsalicylic acid 75 mg / day is recommended for women at high risk of eclampsia from the second trimester of pregnancy to birth.

Antihypertensive therapy aimed at lowering or normalizing blood pressure does not prevent pregnancy complications in women with hypertension. Pregnant women with hypertension are advised to prescribe as few drugs as possible, especially antihypertensives. It is recommended that ACE inhibitors, angiotensin II receptor antagonists, statins and thiazide diuretics be discontinued as soon as possible if the woman is taking them before pregnancy.

In recent years, beta-blockers have become less common in pregnant women. Today it is known that these drugs can cause fetal delay, cause the threat of abortion (non-selective beta-blockers increase uterine tone), and in late pregnancy - to impaired postnatal adaptation of newborns.

Many countries around the world prefer to prescribe a non-selective blocker of alpha- and beta-adrenoceptors - labetalol. In Ukraine, labetalol is recommended for emergency care for pregnant women with hypertension. Labetalol, atenolol, metoprolol - recommended and considered safe for use during breastfeeding.

In pregnant women with hypertension, the appointment is contraindicated:

1. ACE inhibitors; when used in the first trimester of pregnancy in children 3 times more often congenital malformations (especially from the heart and nervous system); when used in the second and third trimesters of pregnancy, there is impaired renal function, dehydration, deformity of the facial skull, contractures, death of the fetus or newborn.
2. Angiotensin II receptor blockers; in many experiments the same adverse effects on the fetus and newborns as in ACE inhibitors are observed;
3. Diuretics; reduce the volume of circulating blood, which impairs the uteroplacental blood supply; strictly prohibited for eclampsia;
4. Reserpine medications; there are data on teratogenic effects, leading to reserpine symptom complex in newborns - gray skin, inhibition, stuffy nose, impaired breastfeeding) when taken in late pregnancy, especially in irrationally increased doses.
5. Progesterone; after the 36th week of pregnancy is contraindicated; causes a high risk of thrombosis in the second and third trimesters of pregnancy, has a high risk of congenital anomaly, penetrates into breast milk defects, including sexual in children of both sexes.
6. Low molecular weight heparins; in some cases, causes rapid (within 2-4 weeks) development of osteoporosis and spinal injuries.

At increase in BP to indicators higher than 170/110 mm of mercury. according to the existing recommendations prescribe labetalol, urapidil - intravenously, clonidine, nifedipine - sublingually or orally.

Sodium nitroprusside - remains the drug of choice, prescribed for a short time due to the risk of adverse effects of cyanides on the fetus.

Glyceryl trinitrate (nitroglycerin) is prescribed in case of severe preeclampsia complicated by pulmonary edema.

Magnesium sulfate is recommended for use during pregnancy under the conditions of prevention or relief of seizures, administered intravenously.

Women with severe gestational hypertension are recommended to conduct certain studies and treatments (Table 3.3)

Patients may be prescribed labetalol, nifedipine and possibly methyldopa.

Table 3.3

Tactics of pregnant women with gestational hypertension

	Degree of hyperemia	
	Hypertension Blood pressure 140 on 90 159 on 110 mm of mercury is severe	**Severe hypertension blood pressure ≥160 / 110 mm Hg. Art.**
1	2	3
Hospitalization	Do not hospitalize	Hospitalize
Antihypertensive therapy	Pharmacotherapy should be prescribed if blood pressure remains above 140 by 90 mm Hg.	If blood pressure is less than 170/110 mm Hg., to lead the patient as in hypertension

Continuation of Table 3.3

1	2	3
Target BP	≤135/85 mm Hg.	≤135/85 mm Hg.
BP measurement	Once or twice a week (depending on blood pressure) until blood pressure reaches 135/85 mm Hg.	Every 15 minutes until blood pressure is less than 170/110 mm Hg.
Determination of proteinuria using indicator strips	Once or twice a week (with blood pressure measurement)	Every time hospitalize
Blood test	Determine the indicators of the general analysis of blood, liver and kidney function at the initial examination, then - weekly	Determine the indicators of the general analysis of blood, liver and kidney function at the initial examination, then - weekly

PIGF-based testing	PIGF-1 testing should be performed if preeclampsia is suspected	PIGF-1 testing should be performed if preeclampsia is suspected
Fetal monitoring	Recommend auscultation of the fetal heart at each reception.	Recommend auscultation of the fetal heart at each reception. Ultrasound of the fetus at diagnosis and repeat every two weeks if severe hypertension persists. Perform cardiography only if clinically indicated.

All side effects and risks of complications of pharmacotherapy for the fetus should be considered when choosing drug therapy.

Labetalol has significant advantages over other b-blockers due to the presence of alpha-blocking properties (vasodilating effect), low penetration through the placenta. No neonates from mothers who started labetalol treatment between 6 and 13 weeks had congenital malformations. The most common side effects are headache and tremor.

Nifedipine may adversely affect the condition of the fetus when administered intravenously or sublingually or at high doses. Sudden or excessive hypotension may lead to decreased uterine-placental-fetal perfusion and therefore fetal distress.

Side effects of nifedipine (swelling of the legs, headache, blood flow to the head, redness of the skin, especially the face, tachycardia, dizziness) are more common in short-acting forms of the drug and are usually observed at the beginning of treatment. It should be borne in mind that the simultaneous use of nifedipine and magnesium sulfate can lead to uncontrolled hypotension, dangerous suppression of neuromuscular function.

Beta-blockers rarely adversely affect the condition of the fetus and newborn. Manifestations of this effect are fetal growth retardation, bradycardia, hypotension, hypoglycemia, respiratory depression. None of the b-blockers is teratogenic. The frequency of delayed fetal growth and low birth weight for gestational age is higher the shorter the treatment begins.

Preference is given to b1-selective blockers (less affecting myometrial b2 receptors) and hydrophilic drugs (less penetrating the placenta). The main side effects of the mother - bradycardia, bronchospasm, dyspepsia, allergic skin reactions, increased contractile activity of the uterus and others. Withdrawal syndrome is typical.

Experience has shown that a significant improvement in maternal and infant termination of pregnancy in patients with hypertension can be achieved by normalizing the magnesium content in a woman's body from a relatively early stage of pregnancy and maintaining it at a sufficient level throughout pregnancy. At the same time there is an improvement in the patient's psycho-emotional state - the feeling of nervous tension, irritability, depression, feelings of anxiety, fear decreases or disappears; sleep improves. In women with a slight increase in blood pressure comes to its normalization. Significantly reduces the number of cases of PE, especially severe, early; miscarriage, fetal disorders, including intrauterine growth retardation. Children are born with more body weight, have better Apgar scores, they are less likely to have asphyxia, malnutrition and other diseases.

To normalize the magnesium content in the body, we use a magnesium-containing drug for oral administration - magnesium-B6, which is prescribed for 2 tablets or 10 ml of drinking solution (content of one ampoule) three times a day. This dose (corresponding to 300 mg of ionized magnesium) provides a normal level of magnesium in the vast majority of patients. If possible, magne-B6 treatment should be started from the 12th to the 14th week of pregnancy and continued throughout pregnancy in all women with hypertension.

Methyldopa - acts on the central mechanisms of blood pressure regulation; penetrates the blood-brain barrier; metabolized with the formation of α-methylnoradrenaline, which in the CNS stimulates postsynaptic α-adrenoceptors of brainstem neurons, which, in turn, leads to suppression of the vasomotor center; hypotensive effect with long-term use is associated with a decrease in total peripheral vascular resistance; minute blood volume changes little; increases the rate of glomerular filtration and renal circulation, reduces the level of renin in blood plasma;

also causes a moderate decrease in cardiac output and heart rate; the effect of the drug is manifested in 2 hours after application and lasts 24-48 hours.

Methyldopa is used to treat hypertension during pregnancy. There is no information about the risk to the fetus with this treatment. Reproductive studies were performed in mice, rats and rabbits using doses that were 1.4, 0.2 and 1.1 times higher than recommended for humans. No negative effect on the fruit was observed. Methyldopa penetrates the placenta to obtain a concentration in the fetus similar to the level in maternal serum.

The Collaborative Perinatal Project monitored only 1 mother-child couple with methyldopa exposure in the first trimester; congenital malformations were not detected.

The Michigan Medicaid recipients monitoring study, which covered 229,101 completed pregnancies between 1985 and 1992, identified 242 newborns exposed to methyldopa in the first trimester of pregnancy. 11 (4.5%) major congenital malformations were registered with an expected 10. Specific data are available for 6 categories of congenital malformations (detected / expected): 1/2 congenital malformations of the cardiovascular system, 1/1, polydactyly, 0/0 spinal cleft, 1/0 facial cleft, 0/0 limb reduction defect, 0/1 hypospadias. These data do not support the association between birth defects and the drug.

After exposure to methyldopa in the first trimester, a decrease in intracranial volume was observed. Examination at the age of 4 did not show an association between smaller head size and mental retardation in children.

A review of 1,157 pregnant women with hypertension did not show an adverse effect of methyldopa treatment. Reported a decrease in systolic pressure by 4-5 mm Hg in 24 infants in the first 2 days after birth.

In one case of taking methyldopa by the mother during pregnancy, a child was born with the following congenital malformations: congenital heart disease, no left kidney, hypospadias. The mother also took clomiphene (a *synthetic ovulation stimulant*) in the first trimester.

According to high-level clinical guidelines, the alpha-blocker prazosin and the central adrenoceptor antagonist clonidine are acceptable during pregnancy (Table 3.4).

Table 3.4

Oral drugs for antihypertensive therapy in pregnant women

Drug	**Initial / maintenance dose**	**Comment**
Methyldopa	125-250 mg / 250-500 mg 2-4 times a day (max. 2 g / d)	There are no data on the maintenance of loading doses of methyldopa
Nifedipine	20-30 mg / 60-120 mg (max. 120 mg / d)	Confidence that the correct dose of nifedipine has been chosen
Labetalol	100 mg / 200-400 mg 2-4 times a day (max. 2.4 g / d)	Contraindicated in bronchoobstructive diseases
Prozazine	0.5 mg / 1 mg (max. 20 mg / d)	Preferably used for pheochromocytoma, not recommended for childbirth

In hypertensive crisis, preference is given to labetalol (IV) and / or urapidil (table 3.5)

Table 3.5

Emergency drugs for hypertensive crisis in pregnant women [1, 46]

Drugs	**Dose and method of administration**	**Features of application**
Urapidil	1-5 ml (5-25 mg) of intravenous urapidil intravenously or 6.25 mg slowly intravenously (for 2 minutes) and then 3-24 mg per hour (using a syringe pump). Maintenance therapy for perfusor - 4 ml of uropidil + 40 ml of 0.9% sodium chloride solution 6-9 mg / hour	Use urapidil 25 mg 5 ml syringe stickers. If after the initial intravenous administration of the drug (25 mg) for two minutes, blood pressure is not reduced by repeated injections (25 mg), you can repeat twice
Labetalol	Initial dose 20 mg (4 ml) for two minutes, maximum 80 mg or 1 to 2 mg / minute, maximum 300 mg. Titrate to stabilize blood pressure by adjusting the injection, every 30 minutes to 32 ml / hour maximum 160 mg / hour)	Use Labetalol 100 mg 20 ml syringe stickers. Contraindicated in patients with asthma, heart disease or congestive heart failure
In resistant hypertension, intravenous clonidine or glycerol trinitrate (nitroglycerin) may be used.		

In the case of joining preeclampsia, the tactics are chosen according to its severity. In the vast majority of cases, childbirth is performed through the natural birth canal. During childbirth provide strict control of blood pressure and heart rate of the mother, monitoring the condition of the fetus.

Drug antihypertensive therapy is started if BP is 160/110 mm Hg. (A), and it is desirable not to reduce blood pressure less than 130/90 mm Hg. for the treatment of hypertension during childbirth use means safe for the fetus and newborn. It is advisable to anesthetize labor in the I and II periods of childbirth (effective prevention of hypertension). The method of choice of anesthesia is epidural anesthesia. In case of impossibility of carrying out epidural anesthesia non-narcotic analgesics, sedatives, fentanyl are used.

In the postpartum period provide careful supervision of a physician (cardiologist), daily blood pressure monitoring, fundus examination, determination of proteinuria, blood tests for creatinine. Preliminary antihypertensive treatment is continued. Lactation is not excluded. Contraindications to lactation and breastfeeding: malignant hypertension, severe damage to target organs. Temporary contraindication - uncontrolled hypertension.

Maternal antihypertensive drug therapy does not interfere with breastfeeding. It is not recommended to use atenolol, clonidine, angiotensin II receptor blockers during lactation. From the group of angiotensin-converting enzyme inhibitors, captopril or enalapril are preferred, they should be prescribed not earlier than 1 month after delivery. It is important to remember that diuretics reduce the amount of breast milk.

Patients with hypertension have pathologies of the hepatobiliary system (51.67%) and urinary system (30%), which increases the number of prescribed drugs (Table 3.4)

Table 3.4.

Pharmacotherapy of patients with hypertension and comorbidity.

The active substance of the drug	**Group**	**Specifics**
Mebeverine hydrochloride	Anticholinergic agent	No interaction study was performed.
Domperidone	Dopamine antagonist. Stimulator of peristalsis	Domperidone is metabolized predominantly by CYP3A4. Contraindicated use with antiarrhythmic drugs of class IA and III. It is not recommended to use with the following CCB drugs: Felodipine, Bepridil, Diltiazem, Verapamil, as these drugs are metabolized by cytochrome P450 CYP3A4 and are its inhibitors, which when co-administered with drugs dromperidone will cause an increase in the latter. It is not recommended to take at the same time in conditions characterized by impaired electrolyte composition of the blood. Use with caution with drugs from the group of loop and thiazide diuretics.
Ademethionine	Amino acids and their derivatives	No clinically significant interactions with drugs for the treatment of hypertension.
Silymarin	Hepatoprotective drugs	Silymarin is an inhibitor of cytochrome P450, it is possible to increase the effect of some drugs.
Ursodeoxycholic acid	Bile acids	Reduces Cmax (maximum plasma concentration) of calcium antagonist nitrendipine. There is an assumption that the drug is an inducer of cytochrome P450 3A4. Drugs that are metabolized by this enzyme require dose adjustment.
Medicines from cranberry leaves, St. John's wort, rose hips, grass trailers.	Drugs for the treatment of urological pathologies	Contains St. John's wort, which is an inducer of cytochrome P-450, which reduces the effects of drugs used in combination.

Aluminum phosphate	Antacid	It has a potassium content of 13.0 - 14.6 mg / package (20 g of gel). Caution is prescribed to patients with renal pathology.
Powder from the pancreas.	Enzyme drugs	No clinically significant interactions were detected.

Enzyme drugs, anticholinergic drugs, dopamine antagonists, hepatoprotective drugs, antacids, bile acid drugs, drugs for the treatment of urological pathologies were prescribed to patients with hypertension and concomitant pathologies of the hepatobiliary and urinary system. Pharmacotherapy with domperidone was performed in 12%, 20% of patients took drugs of the active substance which was silymarin, 12% of pregnant women took a drug containing ursodeoxycholic acid and 22% took local anticides, which increases the risk of adverse drug interactions.

Most drugs do not have significant clinical interactions with drugs used to treat hypertension, but the following features have been identified: domperidone drugs are metabolized by hepatic enzymes - with potent CYP3A4 inhibitors QT interval changes are observed, used with caution with drugs that cause hypokalemia and thiazide diuretics) and bradycardia.

When analyzing the results, it is clear that timely detection of the risk of hypertension in pregnant women makes it possible to avoid abortion, perinatal mortality and effectively control blood pressure.

The conducted researches testify to high efficiency of the improved system of supervision and treatment-and-prophylactic measures at pregnant women with hypertension. Its use significantly reduces the number of cases of combined PE, especially severe and early. Due to this, there is a decrease in the number of premature births, significantly improves the condition of newborns (there were no cases of perinatal losses; children were born with a higher score on the Apgar scale and greater body weight). Given the fact that one third of PE cases in pregnant women in general, according to our data, is due to hypertension, widespread implementation of the developed system of surveillance and treatment and prevention measures will

significantly improve the end of pregnancy for mother and child not only in hypertension but also in population as a whole.

Conclusions.

1. Hypertension during pregnancy is registered in 8-10% of cases and significantly increases the risk of adverse events for both fetus and mother
2. Hypertension in pregnant women can be corrected with pharmacotherapy and lifestyle modifications - healthy eating, weight control, salt reduction in the diet, physical activity.
3. Initial therapy of hypertension is one of the available antihypertensive drugs: methyldopa; beta-blockers; and nifedipine with control of excessive blood pressure reduction. In hypertensive crisis, labetalol (IV) and / or urapidil are preferred.
4. All side effects and risks of complications of pharmacotherapy for the fetus should be considered when choosing drug therapy.

PRACTICAL RECOMMENDATIONS

1. When using drugs for the treatment of hypertension during pregnancy, the target blood pressure is 135/85 mm Hg.
2. For the treatment of chronic hypertension in pregnant women should consider the use of labetalol, if there are contraindications to it, you should consider taking a drug from the group of calcium channel blockers or methyldopa.
3. The high risk of teratogenicity of most antihypertensive drugs requires the doctor to use a limited list of drugs with the use of non-drug therapy, i.e., modification of the lifestyle of pregnant women.
4. The prognosis depends on the level of blood pressure and the presence of complications in pregnant women. Timely start of adequate treatment of hypertension contributes to a good prognosis.
5. The best prevention of hypertension is a healthy lifestyle and diet, as well as the elimination of existing risk factors.

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