Treatment of arterial hypertension in pregnancy

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Abstract

Arterial hypertension is a problem in 7-10% of pregnant women and is related to increased mortality and risk of complications in perinatal period for both, a mother and a child. In the treatment of pregnancy hypertension there are still no agreed and widely approved standards to be followed. Influence of the therapy on both, the pregnant and the fetus, altogether with a lack of large randomized trials lead to conclusion that the optimal solution is a cooperation based on the sum of the experience of gynaecologist, obstetrician, neonatologist and specialists in hypertension. The treatment of hypertension in pregnancy differs in both, pharmacological and non-pharmacological regimens, from the standards established for non-pregnant patients. Weight reduction and increased physical activity are not recommended for women with hypertension who become pregnant. In mild to moderate pregnancy hypertension the non-pharmacological treatment can be enough, providing that sufficient control of the state of both, the mother and the child, is granted. Nevertheless, in case of moderate to severe hypertension pharmacotherapy is indicated and beneficial. Antihypertensives accepted in the management of pregnancy hypertension are alpha-methyldopa, labetalol, β-blockers, calcium channel blockers and hydralazine. Among them only alpha-methyldopa can be used safely during the whole period of pregnancy, which has been confirmed by the long-term clinical observations. In the latest guidelines ESH/ESC from 2007 hydralazine is no longer considered as one of the first line drugs in management of hypertension in pregnancy because of increased risk of perinatal complications reported lately.

Key words: arterial hypertension, pregnancy, treatment

Arterial hypertension is a problem in 7-10% of pregnancies and is a reason for increased risk of perinatal complications including death of a mother or a child [21, 22, 39]. The level of blood pressure during pregnancy has a direct influence on the clinical status of the pregnant women and the fetus. Preterm delivery is a problem in 33% of women with mild hypertension, in comparison to 62-70% in women with severe form of the disease. Intrauterine growth restriction (IUGR) is present respectively in 11% and 40% of those populations [21]. Among various forms of pregnancy hypertension preeclampsia and eclampsia are responsible for most of the serious complications of elevated blood pressure. In USA 15% of mortality rate in pregnant women is caused by hypertension and its complications, second cause of death after pulmonary embolism in this population [22].

Management of hypertension is controversial mainly due to lack of widely accepted standards of treatment in this specific clinical situation. Diversity of proposed classifications, values of blood pressure considered as an indication for treatment, hypotensive drug regimens regarded as optimal are the result of the objective causes (overlap of the pathogenetic factors typical for hypertension and those connected with pregnancy itself, different priorities distribution when taking into consideration the outcome of the mother and the fetus, lack of large, randomized trials because of ethical issues) but also stem from different points of view presented by specialists taking part – gynaecologist, obstetrician, perinatologist and hypertensiologist. A harmonious and efficient cooperation between them can be highly beneficial for both mother and a child facing a threat of hypertension and its complications.

Blood pressure profile in the course of pregnancy

Regardless from presence or absence of arterial hypertension before gestation, in women with normal pregnancy there is a drop in peripheral resistance due to increased activity of local vasoactive substances such as prostacycline and nitric oxide. As a result, value of systolic blood pressure (SBP) decreases 4-6 mm Hg and value of diastolic blood pressure (DBP) – 8-15 mm Hg in the first trimester. Both reach their lowest values around 22-24 week of gestation and then rise gradually to pre-pregnancy level or even higher, at term. Immediately after delivery blood pressure falls down and rises once more in the first 4-5 days of the postpartum period and afterwards gradually goes back to normal non-pregnant level [24]. Except from fall in peripheral resistance during pregnancy, there is also a rise in heart rate (10-15 heart beats/min) and increase in the intravascular volume – reason for a term “hyperkinetic circulation” for the haemodynamics of the cardio-vascular system of a pregnant woman [30].

Measurement of blood pressure in pregnancy

Changes of blood pressure with the advancement of pregnancy suggest that values considered as normal should be different than those in the general population. Nevertheless, the arterial hypertension in gravidity is recognized when SBP > 140 mm Hg or DBP > 90 mm Hg at least twice with the minimum 6 hours’ break between the two measurements [22].

The recommended device for the blood pressure measurement is a mercury sphygmomanometer with the length and width of the cuff adjusted to the circumference of the patient’s arm. The measurement should be performed after at least 10 minutes of rest, in the sitting or left lateral position with the cuff at the level of the heart.

The diastolic value of the blood pressure is considered to be more important predictive factor for the outcome of both, the mother and the child, than the systolic one. According to the recommendations of the European Society of Hyperten-
sion and European Society of Cardiology the diagnostic investigation and therapeu
tic decisions should be based on the value of DBP assessed in the V phase of Korotkoff [13]. In
typical for pregnancy hyperkinetic circulation the appearance of the V phase may even reach the 0 point – than the DBP
should be assessed already in the IV, when auscultation over the brachial artery reveals abrupt muffling of the sound [24].

In recent ESH/ESC guidelines the assessment of blood pressure in pregnant women by automatic 24-hours blood
pressure measurement (ABPM) has been shown to be superior to conventional measurements in predicting protei-
nuria, risk of preterm delivery, infant weight at birth and in general outcome of pregnancy [13].

Classification of arterial hypertension in pregnancy
There are almost a sma
ny classifications of arterial hyper-
tension in pregnancy as scientific societies struggling with the subject. There is a problem with differentiation between chronic hypertension which antedates the pregnancy and hypertension induced by gravidity itself. Frequently, lack of data concerning values of blood pressure before conception and in the first trimester leads to the situation when proper recognition is possible only retrospectively.

Classification of arterial hypertension in pregnancy according to ESH/ESC, 2007 [13]:

- Pre-existing hypertension (chronic hypertension in pregnancy) – hypertension which antedates pregnancy or de-
velops before 20th week of gestation and in most cases persists for more than 42 days post partum; may be asso-
ciated with proteinuria; is present in 1-5% pregnancies [18]. The problem of chronic hypertension in pregnancy will probably increase due to tendency among women to postpone pregnancy until later period of life while the incidence of primary arterial hypertension with age is raising. Among women aged 18 to 29 the pre-existing hypertension is present in 0.6-2% of them and in comparison in population aged 30-39 years old it affects 4.622.3% of pregnant women [21].
- Gestational hypertension (pregnancy induced hypertension) – develops after 20th week of gestation and in most cases resolves within 42 days post partum, with or without accompanying proteinuria; affects 6-17% healthy before pregnancy primigravid women and 2-4% of multi-
para [21].
- Preeclampsia – gestational hypertension with proteinuria > 0.5 g/day; affects 2-7% healthy primigravid women, 14% of twin pregnancies and 18% of patients with preeclampsia in previous gravidity [35].
- Eclampsia – appearance of seizures in the course of preeclampsia (with no sign of other possible expla-
nation such as epilepsy or intracranial hemorrhage).
- Pre-existing hypertension with superimposed preeclampsia (pre-existing hypertension plus superimposed gesta-
tional hypertension with proteinuria) – pre-existing hyper-
tension with further increase of BP and appearing or worsening of proteinuria > 3 g/day in 24-hour urine collection after 20th week of gestation; hypertension does not recede after 42 days from delivery. 10.25% women with pre-existing hypertension is going to have super-
imposed preeclampsia [21]. Risk is higher if there is a co-
existence of kidney failure, when hypertension is present for at least 4 years or was present in previous pregnancy [22].
- Antenataly unclassifiable hypertension – hypertension with or without systemic manifestation, first recorded after 20 weeks of gestation, re-assessment is necessary at or after 42 days post partum.

Main differences among scientific societies in definitions and criteria for recognition of arterial hypertension in pregnancy are presented in table 1.

Simple differentiation between hyper tension disorders in pregnancy, based on presence of proteinuria and the time of onset of hypertension, which might be useful for everyday clinical practice is presented in figure 1.

Management of arterial hypertension in pregnancy

Every pregnant women or planning to become one should have checked her blood pressure regularly. Performing the measurement before 20th week of pregnancy is crucial for the early recognition of the form of pregnancy hyperten-
sion and has its clinical, therapeutic and prognostic implications for the mother and the fetus. The aim of the manage-
ment of hypertension in pregnancy is to diminish the risk which follows for both of them.

In case of recognition of hypertension for the first time during pregnancy in previously healthy woman or not diagno-
sed before, an admission to the hospital unit for a short period of time is recommended to implement the diagnostic procedures for differentiation between primary and secondary hypertension and assessment of the form of pregnancy hypertension as well as the proper management according to achieved results.

Special attention should be paid if risk factors of preeclampsia listed in table 3 are present. Pre-eclampsia is more than hypertension – it is a systemic syndrome where the function of the heart, kidneys, liver, central nervous system and coagulation system is influenced. Preeclampsia is the outcome we want to avoid. Several of its non-hypertensive complications can be life-threatening even when blood pressure elevations are quite mild. For clinical management, pre-
Eclampsia should be overdiagnosed to prevent maternal and perinatal morbidity and mortality — primarily through timing of delivery.

Early baseline sonogram, repeated thereafter with accurate dating and assessment of fetal growth, performing nonstress test or biophysical profile are methods of the fetal assessment in pregnancy, also in women with arterial hypertension. Abnormal uterine artery Doppler together with fetal arterial and venous Doppler ultrasonography seems to be useful predictive factor for development of preeclampsia and further perinatal outcome.

**Laboratory tests for monitoring hypertension in pregnancy**

Adverse influence of hypertension and its complications on the clinical state of the mother and a child is visible in the laboratory assessment of the kidney and liver function and also in the coagulation status. Laboratory tests summarized in Table 2 are helpful in the differentiation between hypertension and other pathological disorders as well as in recognition of the form of hypertension itself, are the indicators of complications and ease the clinical decisions concerning management of the hypertensive state.
Table 3. Risk factors for development of arterial hypertension in pregnancy and preeclampsia [7, 8, 24-26]

<table>
<thead>
<tr>
<th>MATERNAL, non-changeable</th>
<th>MATERNAL, co-morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>age &lt; 18 or &gt; 40 years old</td>
<td>increased BMI (body mass index)</td>
</tr>
<tr>
<td>low socioeconomic status</td>
<td>diabetes</td>
</tr>
<tr>
<td>previous preeclampsia</td>
<td>increased insulin resistance</td>
</tr>
<tr>
<td>primigravity</td>
<td>chronic hypertension</td>
</tr>
<tr>
<td>multigravity</td>
<td>smoking</td>
</tr>
<tr>
<td>family history of preeclampsia</td>
<td>hyperlipidaemia</td>
</tr>
<tr>
<td>low birth weight of the mother</td>
<td>hyperhomocysteinemia</td>
</tr>
<tr>
<td>black race, or Spanish nationality</td>
<td>renal disease (even without significant impairment)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FETAL</th>
<th>PATERNAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>hydatid mole</td>
<td>primipaternity</td>
</tr>
<tr>
<td>hydrops fetalis</td>
<td>limited sperm exposure</td>
</tr>
<tr>
<td>chromosomal anomalies</td>
<td></td>
</tr>
</tbody>
</table>

Possible and safe methods of nonpharmacological management in pregnancy are as follows:
- restriction of physical activity - both at work and at home;
- bed rest in left lateral position;
- light diet, rich in vitamins, microelements and proteins;
- smoking cessation;
- prohibition on alcohol consumption.

There are no proves that restriction of physical activity and prolonged bed rest have a significant influence on the number of complications for the mother and the fetus in pregnancy hypertension [18], [35].

Restriction of salt in diet is not recommended [13]. Women with natrium-sensitive hypertension before pregnancy and significant, beneficial effect of such intervention on values of blood pressure in the past can be an exception.

Several attempts has been made to estimate which one of the laboratory tests has the best predictive value for the risk of developing preeclampsia. It has been noticed that coexistence of raised blood pressure values (> 140/90 mm Hg) with decreased serum renin activity and increased serum uric acid results in 86% risk of preeclampsia. If just one or two of the mentioned are present the risk is 40 or 62% consecutively [21].

Nonpharmacological treatment of hypertension in pregnancy

Pregnancy changes most of the rules for the nonpharmacological management of hypertension. In opposite to non-pregnant patients increased physical activity and restrictions in diet in order to gain lower body mass are not recommended during gestation [13, 20, 22].
Loosing weight in pregnancy is contraindicated, even though obesity is a risk factor of preeclampsia, because during pregnancy it can be harmful for the fetus development (lower birth weight, worse neonatal outcome) [33], [39].

Similarly, increased physical activity during pregnancy is not indicated for the sake of a child [35].

Nonpharmacological management should be recommended for all women with hypertension in pregnancy. Decision whether it is enough or should the pharmacological therapy be added to it depends on the level of blood pressure, week of gestation and presence of risk factors for development of the preeclamptic state.

Prevention of the preeclamptic state – possible interventions

Data concerning the role of calcium supplementation in prophylaxis of preeclampsia are divergent [23]. Recent meta-analysis has shown the reduction in the incidence of severe hypertension and the risk of preeclampsia, followed by the reduction in maternal and fetal mortality and morbidity especially in women at high risk of preeclampsia or with deficiency of this element in diet [2]. Proper ingestion of calcium (2 g/day) in well-balanced diet is advisable regardless of whether gravida has a hypertension or not [2], [22].

Role of the acetylosalicylic acid administered in small doses (75-150 mg/day) has already been established in prevention of preeclampsia and is beneficial especially in women with increased risk of this disease [13, 39]. In women at high risk, aspirin reduces the incidence of preeclampsia (RR = 0.85; 95% CI 0.78-0.92) also the risk of preterm birth before 37th week of gestation (RR = 0.92; 95% CI 0.84-0.97) and mortality among children (RR = 0.86; 95% CI 0.75-0.98) [19]. Compared with placebo, aspirin diminishes the risk of preeclampsia in about 15%, the risk of preterm birth in 8% and perinatal mortality in 14%, with no increase in prevalence of significant bleeding [21]. Small but beneficial effect of the administration of aspirin in high risk group was confirmed by the metaanalysis of Coomarasamy and co-authors [6]. It should be implemented after 12 weeks of gestation (if earlier, there is an increased risk of miscarriage according to data on the use of non-steroid anti-inflammatory drugs) and continued up to delivery.

Up to date, there are no proves from randomized studies and metaanalyses for protective effect of zinc, potassium, magnesium, L-arginine or vitamins (D, E, C, β-carotene) supplementation. Similarly, there are insufficient data to draw reliable conclusions for fish oils, evening primrose oil, administration of glyceryl trinitrate or ozaagrel hydrochloride. They are not recommended in prevention of preeclampsia [13, 37].

Pharmacological treatment of hypertension in pregnancy

Choice of the antihypertensive agent

All antihypertensive drugs are capable of crossing the placenta into the cardiovascular system of the child. That is why lack of adverse effects for the fetus is crucial for the choice of the hypotensive treatment. In pregnancy only those drugs which proved to be safe for the child can be used, there is no class effect while choosing the medication. Otherwise with adverse effects – if there is a negative reaction for one drug only – the whole group is regarded distrusted. The choice of treatment is also dependent on the doctor’s experience with the drug and the gestation period (Fig. 2). In case of pre-existing hypertension the treatment regimen should be changed after conception regarding its influence on the fetus development. Angiotensin converting enzyme inhibitors or angiotensin II type 1 receptor blockers should be withdrawn immediately [13, 15, 22, 32, 39].

Available data do not allow to decide undoubtedly which treatment regimen is the best in mild and moderate pregnancy hypertension [18]. Generally, it is established that the first line treatment should be the alpha-methyldope – a drug which is safe for the child through the whole period of pregnancy and has a low incidence of adverse effects for the mother. The other possibility is labetalol – effective in lowering even high values of blood pressure. The second choice drug should be the calcium channel blockers or beta-blockers. After all hydralazine can be given as a part of polytherapy. In clinical practice the treatment of hypertension in pregnancy is often started with a alpha-methyldope an in case of insufficient blood pressure control the drugs from other groups are added gradually.

In case of severe hypertension when rapid lowering of blood pressure is needed intravenously administered labetalol, orally given nifedypine or alpha-methyldope are preferred. Dilhydralazine and sodium nitroprusside should be avoided because of increased risk of child side effects with such management. Lowering of high blood pressure should be done with caution – rapid decrease may result in hypoperfusion of the uterus and placenta as well as hypoperfusion of the internal organs and central nervous system of the pregnant woman.

Ideal antihypertensive drug should lower the blood pressure to the desired level quickly, with no side effects, but in a controllable manner, should not influence the heart rate, and have beneficial effect on the constriction of the utero-placental vessels.

Groups of antihypertensive drugs and their application during pregnancy

Alpha-methyldope – is centrally acting α2-agonist, acts primarily in the central nervous system, but also stimulates α2 receptors peripherally and decreases arterial pressure by influence on the sympathetic tone. It does not affect the renal blood flow (can be used in case of kidney failure) and the utero-placental circulation (hemodynamics of the fetal cardio-vascular system is not affected). It is an antihypertensive drug of the first choice in case of pregnancy, safe in every trimester, which has been established by the 7,5 years of observation of 195 children from pregnancies with such pharmacological intervention with no adverse outcome on their development [21]. Addition of diuretic in a small dose can be helpful to overcome the problem of resistance to alpha-methyldope, as a solution to overhydration which is an underlying cause of this phenomenon. Alpha-methyldope should be avoided in case of pheochromocytoma because it can change the results of the catecholamine tests [24].

Labetalol – a combined α2- and β-blocker, diminishes the peripheral resistance with mild effect on cardiac output. It is more effective than alpha-methyldope, commonly used in case of moderate to severe hypertension [21]. It is given mainly in the III trimester and during the labour. Transient mild hypertension and bradycardia rarely requiring intervention may occur
in babies born by the mothers treated with labetalol [18]. There are suggestions that in women with preeclampsia labetalol given intravenously during general anesthesia may diminish the tachycardia and hypertensive reaction to intubation [18].

Beta-blockers such as metoprolol may be used as a monotherapy in mild and moderate hypertension, except from the I trimester because of increased risk of bradycardia of the fetus and intraterine growth restriction (IUGR) [12 studies; \( n = 1346 \); RR = 1.36; 95%CI 1.02-1.82] probably due to decreased heart rate or increased peripheral resistance [17]. Later in pregnancy they are as safe and efficient as alpha-methyldopa. Beta-blockers decrease the risk of severe hypertension [11 studies; \( n = 1128 \); RR = 0.37; 95%CI 0.26-0.53], the need for additional antihypertensive drugs [7 studies; \( n = 856 \); RR = 0.44; 95%CI 0.31-0.62] and frequency of hospitalizations [17].

From among calcium channel blockers most frequently used in management of mild and moderate hypertension is nifedypine [21]. Form of 10 mg tablets with prolonged action appears to be better than short-acting capsules, even in case of severe, suddenly rising (> 170/110 mm Hg) hypertension with need for urgent action, because of lower rate of hypotension as a result of the intervention [3]. This group of drugs can also be given sublingually (8 mg s.i.) or intravenously in case of severe hypertension with even better antihypertensive effect than management with hydralazine [5-10 mg i.v.] [19].

Nifedypine acts fast – within 10-20 minutes from oral administration. Given together with magnesium sulphate requires special attention because of highly increased risk of hypotension – dangerous for the central nervous system and the utero-placental circulation [18].

Other frequently used calcium channel blocker is nicardypine. Comparison of labetalol with this drug revealed similar hypotensive effect (20% decrease in BP) with slightly better results and increased rate of mild tachycardia in the calcium channel blocker group [19].

Felodipine is another, newer calcium channel blocker used in pregnancy, which has a selective effect on the vascular smooth muscle cells and decreases blood pressure with insignificant influence on the heart [21].

Calcium channel antagonists should not be used in the I trimester because of data suggesting that they can increase the number of fetal anomalies and should be used with caution whenever given together with magnesium sulphate, as highly increasing the risk of severe hypotension as an adverse effect [16].

Non-dihydropyridine calcium channel antagonist – verapamil is also effective and safe in management of hypertension in pregnancy. It is useful in maintenance treatment when may prevent the tachycardia caused by \( \beta \)-mimetics together with relaxation of the uterine muscular tissue [26].

Hydralazine is an arterial direct vasodilator used usually in polytherapy in the treatment of severe chronic and gestational hypertension, also in eclampsia, preeclampsia and in the hypertension during the postpartum period. Hydralazine can be given parenterally or orally. Recent recommendations ESH/ESC 2007 do not mention hydralazine anymore as a drug of the first choice in the management of hypertension.

### Table 4. Orally administered antihypertensives in pregnancy (acc. to Montan [19] – modified)

<table>
<thead>
<tr>
<th>Antihypertensive drugs</th>
<th>Daily dose</th>
<th>Frequency</th>
<th>Adverse effects for the mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedypine</td>
<td>10-20 mg sl. or orally, repeat after 20-30 min., then 10-20 mg every 3-6h until 1 mg/kg m.c. (max. dose = 50 mg/h; 120 mg/day)</td>
<td>3 × day</td>
<td></td>
</tr>
<tr>
<td>Labetalol</td>
<td>20 mg iv. in bolus, or 20-80 mg every 20-30 min. or iv. 0,5 mg/min. (max. dose = 220 mg/h; 24 g/day)</td>
<td>2 × day</td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>2,5-5 mg iv., repeat after 15-20 min. or i.v. 0,5-10 mg/h (max. dose = 20 mg/h)</td>
<td>3 × day</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>i.v. 5 μg/min., increase every 3-5 min. up to max. 100 μg/min.</td>
<td>2 × day</td>
<td></td>
</tr>
<tr>
<td>Dihydropyridine</td>
<td>30-75 mg i.v. every 30 min.</td>
<td>3 × day</td>
<td></td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>0,25 μg/kg/min., max. 5 μg/kg/min. Not longer than 4 h – danger of intoxication with cyanide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 5. Antihypertensive drugs used in severe hypertension in pregnancy (acc. to Montan [19] – modified)

<table>
<thead>
<tr>
<th>Antihypertensive drugs</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroprusside</td>
<td>25-50 mg</td>
</tr>
<tr>
<td>Labetalol</td>
<td>200-200 mg</td>
</tr>
</tbody>
</table>

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L. Szczepaniak-Chicheł, G. H. Bręborowicz, A. Tykarski
in pregnancy [13]. It is due to increased frequency of perinatal adverse effects when given parenterally. Results of metaanalysis from previous studies suggest that treatment with hydralazine compared with labetolol or nifedipine is responsible for increased incidence of hypotension (13 studies; RR  3.29; 95%CI 1.50-7.23) and oliguria in pregnant patients (3 studies; RR  4.0; 95%CI 1.22-12.50), increased risk of premature placental ablation (5 studies; RR  4.17; 95%CI 1.19-14.28), necessity for cesarean section (14 studies; RR  1.30; 95%CI 1.08-1.59) and lower score in the Apgar scale in the first minute of the newborn’s life (3 studies; RR  2.70; 95%CI 1.27-5.88). Compared with labetolol only the frequency of newborns’ bradycardia was lower in the hydralazine group (RD  0.24; 95%CI  -0.42 to  -0.06) [16]. There are data suggesting that hydralazine given during pregnancy for a longer period of time may induce lupoid-like syndrome and thrombocytopenia in the newborn. Also other adverse effects of hydralazine like nausea, vomiting or headache in pregnant woman may be misleading – they suggest worsening of the clinical state of the patient due to hypertension itself, even with the transformation of pre eclampsia into eclampsia. Even though, hydralazine is still used and useful in clinical practice mainly because of wide and of many years standing experience of the gynecologists and obstetricians with this drug.

Diuretics can be used as an antihypertensive only if given as a continuation of the preconceptional treatment lasting before pregnancy for a longer period of time [26]. Metaanalysis of Collins and co-workers encompassing over 7000 patients treated with diuretics did not reveal any significant risk for pregnancy period [5]. Nevertheless, because of the theoretical premises implementation of antihypertensive treatment with diuretic for the first time during pregnancy is not considered to be accurate. Decrease of intravascular volume, already diminished in gestational hypertension, with further impairment of the uteroplacental blood flow may lead to intraterine growth restriction [31]. Diuretics are indicated in pregnancy only in specific situations such as severe heart failure, pulmonary edema [39] or oliguria [13].

Angiotensin converting enzyme inhibitors (ACE-I) and angiotensine II receptor type 1 blockers (ARB) are continued during pregnancy and lactation because of possible adverse effects on the child’s health such as: intruterine growth restriction, hypoplasia of the lungs, oligohydramnios, kidney failure (temporaty in case of the newborn after telmisartan therapy; permanent after ACE-I therapy of chronic hypertension in the mother in II and III trimester) and increased perinatal mortality (5 death cases) [4, 14, 19, 31, 39].

Sodium nitroprusside – dilatation of the vessels, both veins and arteries is responsible for antihypertensive action. The drug is nowadays gradually withdrawn from the market, in pregnancy was used rarely, only in hypertensive crisis when other possibilities failed, always under control of the cyjanide levels in the blood serum and not longer than for 4 hours (danger of the intoxication of the fetus) [19].

Management of pre-existing arterial hypertension in pregnancy

There is a lack of unanimity between recommendations of different scientific societies concerning the level of blood pressure at which pharmacological treatment should be implemented in pre-existing hypertension. There is a wide spectrum of views on the subject – from treatment of every patient with BP > 140/90 mm Hg [39], to regarding as the indication for intervention only the severe form of hypertension (> 180/110 mm Hg) [15].

It seems rational to take into account not only the values of BP but also the form of hypertension in pregnancy, number and severity of risk factors, data from the history of the patient, present state of the mother and a child and possible side effects of the therapy [13]. Antihypertensive treatment is indicated and beneficial in severe form of hypertension (according to European recommendations the cut-off point is at 170/110 mm Hg [13], and according to North American – at 160/110 mm Hg [32]). In mild and moderate forms of hypertension necessity of treatment in pregnancy is controversial.

In mild pre-existing hypertension without proteinuria antihypertensive treatment do not diminish the number of complications (superimposed preeclampsia, preterm delivery, preterm placenta detachment and mortality) [14]. According to data from metaanalysis of Magee and co-authors pharmacotherapy of mild pre-existing hypertension decreases the prevalence of severe forms of hypertension (> 160/100 mm Hg), but with no significant effect on its complications for the mother and a child. None of the antihypertensives seemed to be more effective or beneficial in this analysis [18]. Similarly, metaanalysis of 40 studies (3797 women) concerning mild and moderate hypertension showed the reduction in prevalence of severe form of hypertension (17 studies, 2155 women; RR  0.52 (95%CI 0.41-0.64; NNT  9-17)) with no reduction in prevalence of preeclampsia (19 studies, 2402 women; RR  0.99 (95%CI 0.84-1.18), neonatal mortality (23 studies, 2727 women; RR  0.71 (95%CI 0.46-1.09)), preterm delivery rate (12 studies, 1738 women; RR  0.98 (95%CI 0.85-1.13)) or intruterine growth restriction (17 studies, 2159 women; RR  1.13 (95%CI 0.91-1.42)). Also none of the antihypertensive agents seemed to be better than the others [1].

Harm for the mother’s cardiovascular long-term outcome is insignificant when dealing with relatively short, 9-month period without appropriate hypertensive treatment. On the contrary – the harm for the baby connected with adverse effects of treatment and iatrogenic hypertension is huge [33].

Based on data given above it is advised to diminish or even withdraw the antihypertensive pharmacological treatment in women with mild pre-existing hypertension without superimposed proteinuria, especially in the I trimester when the BP values might be even lower than those before conception [7]. Further management in this group is based on BP monitoring and assessment of the clinical state of the mother and a child. In women with complicated, long-lasting hypertension treated with three or more drugs before pregnancy it is advised to modify therapy without withdrawal if antihypertensives are necessary to maintain blood pressure within the norm [34]. Values above 160/100 mm Hg are indication for treatment intensification.

The metaanalysis performed by Duley and co-workers was aimed at the assessment of the efficacy and safety of different antihypertensives. It included 20 studies with overall number of 1637 women with severe hypertension. It revealed that diltiazem and ketanserin should not be used anymore.
because of episodes of severe hypertensive requiring treatment in case of the first one and a lack of appropriate hypertensive effect in comparison to hydralazine for the other. Authors of the metaanalysis conclude that the choice between available antihypertensives, except from the two mentioned above, should be based on the individual clinical experience, because there is no proof that any of them is better or worse than the rest [10].

Management of gestational hypertension or antenatally unclassifiable hypertension

In women with gestational hypertension or hypertension unclassified before delivery with values of BP < 150/100 mm Hg non-pharmacological treatment is enough. In case of higher BP additional pharmacotherapy should be considered. Proteinuria, target organ involvement, symptomatic hypertension, history of gestational hypertension in previous pregnancies indicate that pharmacotherapy should be implemented earlier – when BP is ≥ 140/90 mm Hg, similarly as it is for the pre-existing hypertension in pregnancy [35].

Management of preeclampsia

Coexistence of proteinuria > 500 mg/day with arterial hypertension which appeared in pregnancy after 20th week of gestation is called preeclampsia. In some cases such symptoms like headache, blurred vision, stomachache, incorrect values of laboratory findings instead of proteinuria can also be a signal of the worsening of the clinical state.

Increase in the SBP ≥ 30 mm Hg or DBP ≥ 15 mm Hg, peripheral oedema and increase in body mass are no longer considered to be the diagnostic criteria of preeclamptic state but if present also demand more careful clinical observation [13, 24, 39].

Preeclampsia is responsible for 15% of preterm deliveries, which are the main cause of increased neonatal mortality, especially in countries with low socio-economic status [25]. Still, even in highly equipped centers preeclampsia and its complications remains a serious problem. Preeclampsia can be mild or severe [26].

Diagnostic criteria for mild form of preeclampsia:
- SBP > 140/90 mm Hg in at least two measurements;
- proteinuria > 500 mg/24 h.

Diagnostic criteria for severe form of preeclampsia:
- SBP > 160 mm Hg or DBP > 110 mm Hg;
- proteinuria ≥ 2.0 g (+2 or +3 in the dipstick test) – without coexisting urinary tract infection, no history of proteinuria before pregnancy;
- serum creatinine > 1.2 mg/dl;
- PLT > 100 000/mm³ and/or microangiopathic hemolytic anemia (with increased serum LDH);
- serum uric acid > 3.6 mg/dl;
- ARO < 4 ng/ml/h;
- increased serum ALT and/or AST;
- persistent headache, blurred vision or other neurological symptoms;
- persistent stomachache, nausea, vomiting.

In case of mild preeclampsia bed-rest, avoiding physical activity and stress are recommended with regular assessment of the BP values and the clinical state of the mother and a child even as an ambulatory management if the patients compliance is proper [35].

In case of severe preeclampsia hospitalization is necessary. Usually the state of the pregnant woman gradually deteriorates and the final solution is induction of the delivery. Through the optimal antihypertensive and anticonvulsant therapy it is possible to postpone this moment until the child is ready to be born [30]. In case of preterm induction of the delivery between 33-34 week of gestation it is advisable to accelerate the maturation of the surfactant by administration of glucocorticosteroids 48 hours before delivery – if the state of the mother and the fetus is stable enough to prolong the pregnancy for two more days [28, 35].

Management of eclampsia

Eclampsia may appear in pregnancy (38-53%), during delivery (18-36%), and also in the postpartum period (11-44%), usually in the first 48 hours. Most of the cases (91%) appear in the first 28 weeks of pregnancy, only in 7.5% of women between 21-27 week and in 1.5% cases before 21st week [37].

Except from early recognition of preeclampsia there are no other prodromal symptoms and signs of forthcoming eclampsia, although there are some attempts to use the values of blood pressure within the intracranial vessels assessed by ultrasound methods as a predictive ones [19].

Treatment of eclampsia is based on the anticonvulsant therapy with optimal antihypertensive treatment to lower the values of blood pressure to the safe level of SBP 140-160 mm Hg and DBP 90-110 mm Hg. Antihypertensive drugs used in severe hypertension in eclampsia are mainly labetolol, dicyclomine and nifedipine (Table 5) [30].

Preferred anticonvulsant drug in prevention and treatment of seizures in eclampsia according to surveys and metaanalises is magnesium sulphate [9], [35], [38]. In order to stop the seizures and prevent the recurrent ones it is recommended to inject 36 g (30-60 ml of 10% MgSO₄ solution) slowly intravenously (during 5-20 minutes) with following infusion of 1-2 g/h. 10% of those women will have recurrent attacks – it is possible to give once more 2 g of magnesium sulphate solution in injection lasting for 3-5 minutes. Maximal daily dose of magnesium sulphate is 2024 g. Other anticonvulsants used in clinical practice are fenytoine (iv. infusion 50 mg/min.) and diazepam (5-10 mg iv., afterwards 20 mg i.m. every 6 hours) [37].

HELLP syndrome (haemolysis, elevated liver enzyme levels and low platelet count)

Coincidence of haemolysis, elevated liver enzyme levels and low platelet count in pregnant women is called HELLP syndrome [40]. It seems to be the multi-organ manifestation of severe preeclampsia or eclampsia, although 15% of women with this syndrome have normal values of blood pressure with no proteinuria [36].

HELLP syndrome is a severe state with high mortality rate and complications such as: pulmonary oedema, DIC, ARDS, acute kidney failure, sepsis, liver failure or liver hemorrhage, stroke, premature detachment of the placenta, and all possible afteraths for the child of the premature birth [18, 27, 29, 36].
Treatments of arterial hypertension during lactation

According to available data, antihypertensive drugs appear in the milk of a breast-feeding mother [41]. Data on safety of antihypertensive treatment during lactation are scarce, there are no long-term observations. It seems that alpha-blockers, methyldopa and hydralazine are safe for the child, and in case of metoprolol or metaraminol they can be administered [26]. There are no data concerning safety of nifedipine [26]. Diuretics may reduce milk volume and suppress lactation, ACE-I and angiotensine receptor blockers damage kidney function of the newborn – those groups of antihypertensives are contraindicated [22].

To summarize – it is recommended for breast-feeding mothers to continue the therapy with drugs considered to be safe during pregnancy.

As it is underlined in the recent ESH/ESC guidelines women with previous gestational hypertension seem to be at increased risk for cardiovascular disease in later life. It may depend on relative hyperandrogenic state and further alterations in endothelial function, carbohydrates and lipid metabolism which have been shown in otherwise healthy women with history of gestational hypertension [13].

References


